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1. Russek, H. I.; Urbach, K. F.; Doerner, A. A., and Zohman, B. L.: J.A.M.A. *153*:207 (Sept. 19) 1953.
2. Humphreys, P., *et al.*: Angiology 3:1 (Feb.) 1952.
3. Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952.


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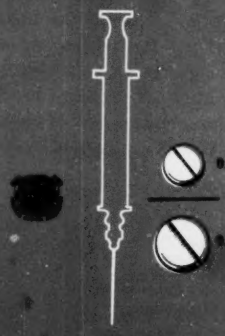


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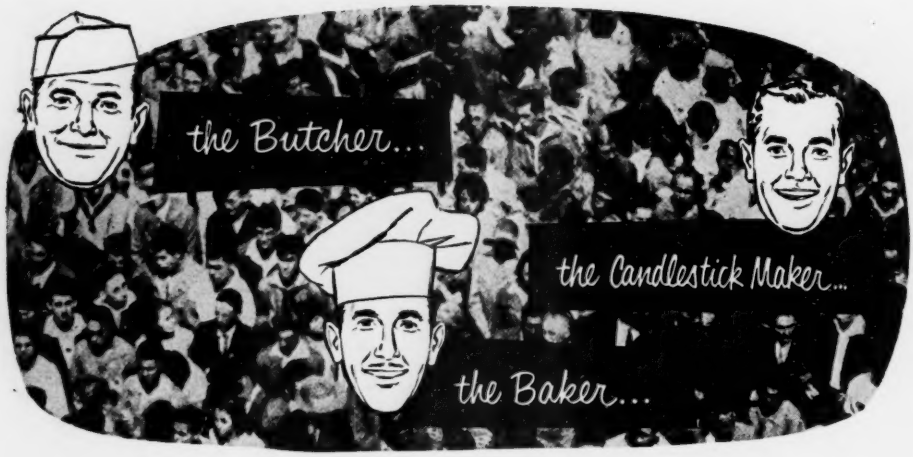


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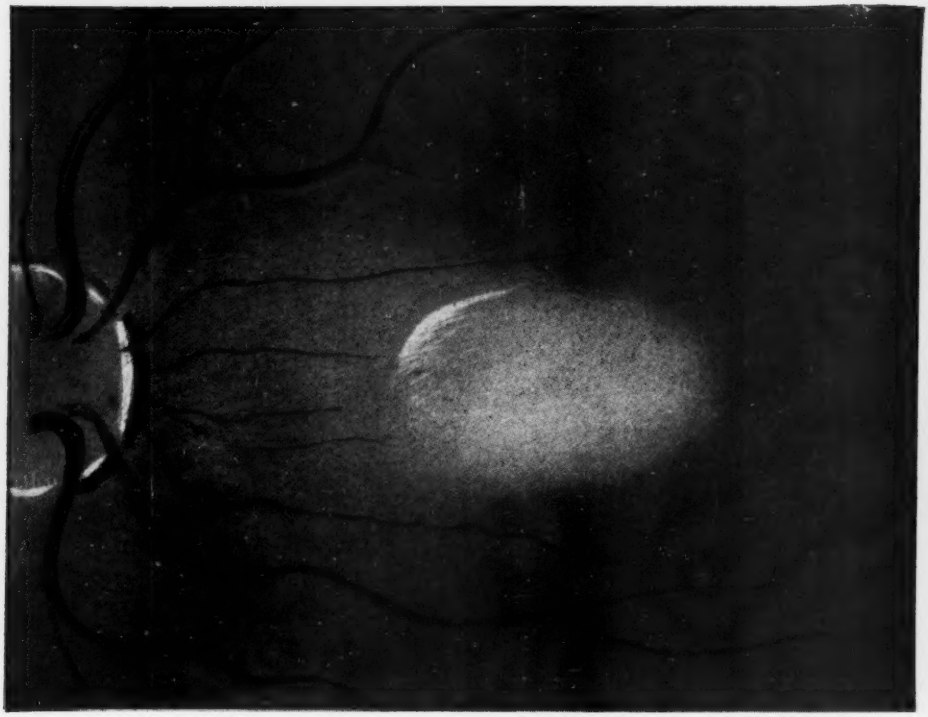

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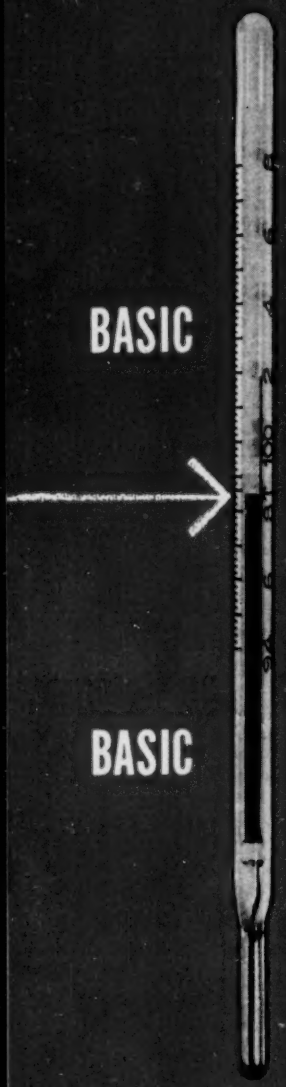

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# VISCERAL EPILEPSY

DONALD W. MULDER, M.D.
DAVID DALY, M.D.
AND
ALLAN A. BAILEY, M.D.
ROCHESTER, MINN.

GASTROINTESTINAL, genitourinary, and cardiorespiratory symptoms may occur as presenting complaints in patients who have epileptic disorders. These symptoms are often misunderstood, and localized visceral disease may be diagnosed or the bizarre nature of the complaints may lead to the diagnosis of a psychiatric condition. The prompt recognition and differentiation of these symptoms are of great therapeutic significance.

The presence of visceral symptoms as a manifestation of convulsive disorders has long been recognized. Morgagni,[1] in his textbook published in 1769, reported the case of a 68-year-old priest whose epileptic attacks began with pain in the right hypochondrium followed by nausea and vomiting. Trousseau,[2] in his textbook published in 1873, described in great detail the symptoms of visceral epilepsy and its differential diagnosis from cardiac and abdominal disease. Jackson [3] discussed the visceral manifestations of epilepsy. More recently, Penfield and Kristiansen [4] have demonstrated that such symptoms may result from localized irritation of the cortex and may be precipitated by electric stimulation of specific regions of the cortex.

Visceral aurae in epilepsy are frequent. Gowers [5] reported that 17.7% of a large series of epileptic patients described visceral aurae. Lennox and Cobb [6] reported that 14.6% of their series of 1,527 patients who had epilepsy described visceral aurae. Clinically, Moore,[7] as well as others, has stressed the occasional difficulty in differential diagnosis of paroxysmal abdominal symptoms that are secondary to epilepsy.

Visceral phenomena are present in most epileptic attacks. The frequent insistence of the epileptic patient that his symptoms are related to visceral disease is undoubtedly a consequence of the common occurrence of these symptoms as an important part of his attack. In grand mal the visceral symptoms are so overshadowed by the motor phenomena that they are usually ignored. In petit mal the disturbance of consciousness is the most prominent feature of the brief attack, although visceral manifestations, such as pallor or urinary incontinence, may be observed.

From the Sections of Neurology and Psychiatry, Mayo Clinic.

Read at the meeting of the American Psychiatric Association, Los Angeles, Calif., May 6, 1953.

PRESENT STUDY

This is a report on the visceral symptoms described by 100 patients encountered at the Mayo Clinic. These symptoms occurred either as an aura to the epileptic attack or as the attack itself. The visceral symptoms were an important part of the presenting complaints in all these patients. The diagnosis of convulsive disorder was verified by observation of an induced or spontaneous attack, or on the basis of electroencephalographic findings, or from evidence in the history. Of these patients, 45 were female and 55 were male; the ages ranged from 11 to 67 years. The paroxysmal symptoms varied in duration from 4 months to 29 years. These patients were examined neurologically and all but two of them had electroencephalograms. Angiograms, pneumoencephalograms, or ventriculograms were made when necessary.

Eighty-three patients had evidence of a focal cerebral lesion that served as a source of abnormal electric discharge and appeared to be the cause of the attacks (Table 1). Of this group, 75 patients had a focus in one temporal lobe; the lesions

TABLE 1.—*Cerebral Lesions in 100 Patients Who Had Visceral Epilepsy*

| Location | Confirmation | | Total |
|---|---|---|---|
| | Surgical | Pneumogram or Electroencephalogram | |
| Temporal lobe | 21 | 54 | 75 |
| Anterior parasagittal region | 5 | 0 | 5 |
| Frontal lobe | 1 | 0 | 1 |
| Occipital lobe | 0 | 1 | 1 |
| Parietal lobe | 1 | 0 | 1 |
| Total | 28 | 55 | 83 |

were found either by electroencephalography or at surgical exploration. Localization occurred once in a frontal lobe, once in an occipital lobe, and once in the parietal region. Three patients had tumors in the frontal parasagittal regions and in the two remaining patients of this group lipomas arose in the corpus callosum and involved the frontal parasagittal regions bilaterally.

Thirty-two patients had tumors of the brain. These lesions included 21 astrocytomas, 2 angiomas, 2 meningiomas, 2 lipomas, 1 oligodendroglioma, and 1 neuroganglioma. Three patients had surgically inaccessible tumors of unknown histologic type. One additional patient had a porencephalic cyst.

One or more electroencephalograms were done for 98 patients. In 14 patients the records were normal. Focal abnormalities in the temporal regions were found in 67 patients. In 31 patients a focus giving rise to slow spikes was found, and in 37 patients a focus causing random slow waves was seen. Abnormality in both temporal lobes was observed in 10 patients. In records of four of these patients slow spikes occurred independently in both temporal lobes; in two random slow waves were noted, and in four rhythmic waves having a frequency of 4 to 7 cps were observed. One of the patients had rhythmic slow discharges arising synchronously in both occipital regions. Four patients had rhythmic discharges at the rate of 4 to 7 cps that appeared to originate from all regions of the head. Focal occipital discharges were observed in one patient.

Generalized convulsions were reported by 50 patients in this series. These convulsions occurred either once or many times and in some instances always followed the visceral symptoms. Paroxysmal psychopathologic phenomena associated with visceral disturbances were described by 46 patients. These included hallucinations, automatisms, illusions, and disturbances of mood and perception. Careful observation frequently revealed other paroxysmal disturbances associated with the visceral symptoms. These included chewing movements, minor alterations of consciousness, and, occasionally, clonic or tonic movements of an extremity.

This report is limited to those paroxysmal visceral symptoms of which the patient complained and does not include certain objective phenomena that may be observed by trained physicians, except in those instances in which such objective findings have appeared to be particularly significant. Considerable overlapping of visceral symptoms was noted, so that a patient frequently complained of symptoms that involved more than one visceral system (Table 2). We have not attempted to list the presenting symptom in these attacks, because in our experi-

TABLE 2.—*Incidence of Paroxysmal Symptoms in 100 Cases of Visceral Epilepsy*

| Symptoms | Cases, No. |
|---|---|
| Visceral | |
| Gastrointestinal | 65 |
| Cardiorespiratory | 50 |
| Genitourinary | 5 |
| Rising visceral sensations | 17 |
| Generalized convulsions | 50 |
| Psychiatric disturbances | 46 |

ence this initial symptom frequently varied. That is, the general pattern of the attack remained the same in each patient, although the initiating symptom might vary in different attacks.

In a general way these symptoms could be classified as either motor or sensory visceral phenomena. It is obvious that excessive salivation, vomiting, belching, and borborygmi are primarily motor phenomena. Abdominal discomfort usually was considered to be a manifestation of central sensory stimulation, although it was recognized that abdominal pain might at times be secondary to contraction of the intestine. In the majority of instances it was not possible to differentiate motor and sensory symptoms with certainty; both types usually occurred in the same attack.

### GASTROINTESTINAL SYMPTOMS

Sixty-five patients described symptoms that suggested involvement of the gastrointestinal tract (Table 3). Nausea was the most frequent gastrointestinal symptom; 38 patients experienced it during their paroxysmal attacks. Frequently nausea was present alone, and often it occurred paroxysmally many months before the onset of overt convulsive attacks. In a few instances paroxysmal nausea was the first symptom of brain tumor, but it was not considered to be secondary to increased intracranial pressure. Nausea was commonly associated with vomiting, belching, borborygmi, and, rarely, with involuntary defecation without loss of consciousness. These latter symptoms, when present, were invariably associated with nausea. The vomiting was not projectile.

CASE 1.—A 24-year-old man had noted symptoms for 21 months prior to our examination. Initially they consisted of brief paroxysmal nausea and a bitter taste that recurred frequently in the first five months. Later, these initial sympoms were followed by numbness in the right arm and leg and a sensation of his being in the wrong place. Shortly before our examination, generalized convulsions appeared. A left carotid angiogram confirmed suspicions of a left frontotemporal expanding lesion. Surgical exploration revealed an astrocytoma, Grade 3, of the left cerebral hemisphere, involving the posterior portion of the frontal lobe and the anterior portion of the temporal lobe.

CASE 2.—A 58-year-old man had experienced three or four generalized convulsions and numerous minor attacks. The paroxysms were initiated by a sensation that "I'm sick in my bowels." Borborygmi would be present, followed by "burning" of the bowel and defecation; the latter was involuntary, although the patient was conscious. During this time the patient would be apprehensive and tense. Occasionally he had a "heavy" feeling that he localized to the lower abdominal quadrants. He stated that he could speak during the aura. On one occasion he recovered consciousness 100 yd. (91 meters) from where the attack began. After attacks, he sometimes noted generalized soreness in his muscles. His speech would be incoherent, and he would not know where he was. Since the onset of these episodes the patient had experienced attacks in which he would note borborygmi and then, if he closed his eyes, "bad visions of fights and murders." The electroencephalogram showed rhythmic discharges from the left sylvian region at a frequency of 6 to 7 cps. Some of these had the form of a slow spike that was repeated rhythmically.

TABLE 3.—*Incidence of Gastrointestinal Symptoms in 100 Cases of Visceral Epilepsy*

| Symptoms | Cases, No. |
|---|---|
| Nausea | 38 |
| Abdominal discomfort | 31 |
| Vomiting | 9 |
| Borborygmi and belching | 4 |
| Involuntary defecation | 4 |
| Salivation | 8 |

Abdominal discomfort was described by 31 patients. This was usually described as a strange or unreal sensation. It might be associated with a disturbance in mood, and the patients used such terms as "fear or anger in the belly." It was most commonly described as an "all-gone feeling," a "cramplike feeling," a "feeling like a ball rolling in my stomach," or a feeling "like my stomach turned upside down." This symptom was usually paroxysmal and persisted for a brief period, rarely longer than a minute.

CASE 3.—A 25-year-old woman had experienced convulsions since the age of 15 months. She described the minor spells as follows: "I get a funny feeling, a feeling right in the abdomen, sort of a small circle. If you inhale, it seems that the circle gets bigger as you inhale. If you exhale, it stays the same; nothing happens. After breathing about seven or eight times it gradually decreases instead of increasing. Your heart beats much faster. You can feel it happening. You don't feel frightened. There is no emotion. Everything looks normal, and I think clearly. I guess that is about all unless it is going to be a severe attack and then you pass completely out and don't know what happens." The patient's mother noted that during the attacks she became pale and salivated profusely without masticatory or swallowing movements. After the attack the patient would have no appetite whatsoever. No food would appeal to her; the odor of food would be normal but not the taste. In the next few days, because of lack of appetite, she would lose 4 or 5 lb. (1.8 or 2.2 kg.). Minor attacks occurred as often as 10 times a day and were aggravated at menstrual periods. During major attacks she had generalized convulsions with associated urinary incontinence. During minor attacks she occasionally had transitory amnesia for part of the episode. The electroencephalogram showed discharges of 4 to 7 cps arising from both temporal regions.

Occasionally, the abdominal discomfort was described as "pain." Usually careful interrogation revealed that the patient had described an unusual abdominal sensation as "pain." However, if pain was present it usually occurred high in the epigastrium and was described as "burning" or "cramping." It was frequently associated with disturbances in vasomotor function and pulse rate, so that the patient may become cyanotic and have bradycardia. Since these symptoms occurred paroxysmally as manifestations of convulsive disorders, they may lead to some difficulty in differential diagnosis. In a few instances we have encountered patients who have had abdominal operations because of these unrecognized epileptic disorders.

CASE 4.—A 16-year-old girl had suffered from recurrent attacks, all following the same pattern, since she was 5 years of age. The attacks began with an abrupt intense pain high in the epigastrium. She described it as being "like a knife." Her heart felt as if it were pounding—"like I've been running." During the attack she had been told that she became pale. No nausea, retching, or borborygmi were noted. She thought that she breathed normally and that she could speak. She never had been incontinent. The pain lasted only a few seconds, after which she behaved in an automatic fashion. She stared, clasped her hands, and might at times talk fairly rationally, although afterwards she was amnesic for what she had said. She might carry out purposeful activity; on occasions she had walked as far as two blocks without recalling what she had done. After the attack she was sleepy and nervous. She never had experienced a generalized convulsion. At times she had had as many as four or five attacks per day, although since the institution of treatment she had usually noted only one per week.

Results of physical and neurologic examinations were within normal limits. Part of an attack was witnessed during the examination. The observer came in after the attack had begun and found that the patient was staring. The pupils were of average size; the pulse rate was 80, and no pallor or sweating was present. Her hands were clasped, and she would not respond. She stood up and sat down, then clasped and unclasped her hands several times. The duration of the attack was two minutes. For the next three or four minutes postictal confusion was noted but no aphasia was present. Roentgenograms of the head disclosed nothing abnormal. An electroencephalogram showed rhythmic slow waves and frequent slow spikes appearing from electrodes placed in the region of the right sylvian fissure and the right ear. Pneumoencephalography and angiography were proposed, but the patient decided to defer such studies.

Excessive salivation was occasionally observed in these attacks. It was usually associated with chewing movements and often with paroxysmal psychiatric disturbances. Patients may have a disturbance in appetite as a prodrome to an attack. Hunger has been reported occasionally as a prodrome.

CASE 5.—A 25-year-old woman had been seen at the clinic on a number of occasions. She began having convulsions in infancy and had continued to have them intermittently. Originally the patient observed that preceding a seizure she could think exceptionally rapidly and had an enormous appetite. Recently the attacks had been less severe. They now began with a queer sensation like a "quivering" in her heart, and then suddenly she would lose consciousness momentarily. She might swallow frequently just before a spell. Afterwards she felt chilly and might have "goose pimples." The seizures occurred every two to three days and lasted three to four seconds. An electroencephalogram revealed mild nonfocal abnormality. Administration of pentylenetetrazol (Metrazol) produced a typical attack, during which an electroencephalogram showed sharp waves arising from the region of the left sylvian fissure.

CASE 6.—A 56-year-old man had experienced convulsions since the age of 34 years. One year prior to the onset of the seizures, he had had severe pneumonia with associated coma. His attacks would begin with an aura lasting 20 minutes, during which he had an epigastric sensation. No nausea was noted. He perspired profusely and noted that often his bed was drenched with sweat. He said, "I always do a great deal of belching. If I were alone, I would do more but my wife gives me 'Hail Columbia' when I start belching." The patient often tried to make himself vomit by putting his finger down his throat. He stated, "It helps a great deal. I sometimes

avoid an attack by belching and getting a pan and throwing up." During the aura the patient saw a "vision of little men. It seems as though they are out in front of me at that time, but at the same time I can feel them as though they are dancing on my stomach. They are dancing up and down regardless of whether I am lying down or standing up. They look as if they were living people, not animated. These men were part of a joke. It seems like my first connection with them goes back to early jokes, probably fifty years ago. They have on long, black capes and large floppy hats." During the attack the patient had a "sour or gassy taste" that appeared to come up in the back of his mouth. His wife stated that he turned white. At the end of the aura, the patient would have a generalized convulsion with sudden loss of consciousness, rigidity, and clonic movements of all extremities. He bit his tongue and had urinary incontinence. On occasion he had injured himself during the seizure.

The electroencephalogram showed episodic slow discharges from electrodes placed in the region of the left sylvian fissure and the left ear. Roentgenograms of the head were normal. The cerebrospinal fluid contained 5 lymphocytes per cubic millimeter; the value for protein was 45 mg. per 100 cc. Roentgenographic examination of the stomach and duodenum showed nothing abnormal.

TABLE 4.—*Incidence of Cardiorespiratory and Autonomic Signs and Symptoms in 100 Cases of Visceral Epilepsy*

| Symptoms and Signs | Cases, No. |
|---|---|
| Palpitation | 11 |
| Thoracic distress | 4 |
| Hyperventilation | 3 |
| Vasomotor | 38 |
| Blanching | 29 |
| Flushing | 11 |
| Miscellaneous | 19 |
| Sweating | 14 |
| Pilomotor | 2 |
| Other | 4 |

### CARDIORESPIRATORY SYMPTOMS

Symptoms referable to the cardiorespiratory system were reported by 50 patients (Table 4). Respiratory symptoms are infrequent complaints. In most major seizures, respiratory arrest is a prominent feature of the attack. In minor episodes, respiratory arrest may be the most prominent single manifestation of the attack. Many years ago Jackson [8] described arrest of respiration with the thorax expanded and postulated that this was secondary to a lesion of the temporal lobe. Less frequently hyperventilation occurs as part of the attack. Three of the patients in this series complained of hyperventilation that was either an aura to an attack or the attack itself. These episodes of hyperventilation did not appear to be the reaction of a neurotic person to an anxiety-producing situation; rather, the hyperventilation apparently was a symptom of focal cerebral stimulation.

Cardiac symptoms were described in great detail. This may be a reflection of the concern of the average patient about his cardiac function and may explain the frequent assumption on the part of the patient and his physician that these attacks are related to cardiac dysfunction. The most frequent cardiac symptoms described were palpitation and thoracic distress. The latter was frequently described as a substernal "pressure" or "strange feeling." The palpitation was associated often with an observable increase in pulse rate. The patients described it as a rapid pounding or beating of the heart. Conversely, extensive bradycardia was noted

in some patients during an attack; this at times was associated with a decrease in blood pressure. The latter effect may account for the sensations of faintness associated with the attacks. Pain in the thorax, as in the abdomen, was an infrequent complaint; it was observed in three patients.

CASE 7.—This 34-year-old man described his attacks as beginning with a "pressure" of crushing intensity, high in the epigastrium, that "worked up under the breast bone." This sensation lasted three or four seconds and was followed by blinking and unconsciousness. After these attacks the patient noted a dull, burning, precordial pain that extended into the left shoulder and down the left arm to the wrist. Associated with this was severe headache. Hyperventilation reproduced the pain; however, an electrocardiogram showed nothing abnormal. A pneumoencephalogram revealed defective filling of the left anterior horn of the lateral ventricle, with a mass extending into the lateral and inferior portions of the left frontal horn, just posterior and contiguous to the foramen of Monro.

CASE 8.—A 56-year-old woman complained of thoracic distress with episodic loss of consciousness. The attacks had been present for seven years. As these episodes began, she felt as though her head were swelling; things became "blurry." Next, a "choked" feeling was noted in the epigastrium, with severe nausea, followed by a feeling of heavy "pressure" in the thorax. Generalized convulsions then occurred. After the attack was over, abdominal pain continued until she vomited. She might be drowsy for a short time. In the past she had experienced as many as two attacks a week, but since treatment had begun she had had none for several years.

Results of physical and neurologic examinations were normal, as were results of routine laboratory studies. Roentgenograms of the head showed nothing abnormal. Roentgenographic examinations of the esophagus, stomach, duodenum, and gall bladder were normal. The electroencephalogram showed diffuse abnormalities.

Vasomotor phenomena are rarely described by these patients. Frequently such occurrences are reported by relatives, who note transient blanching, flushing, or cyanosis during an attack. Blanching is particularly frequent and is often associated with nausea. Less frequently, flushing of the face or upper extremities may be observed. In some instances, change in color apparently is secondary to disturbances in respiration, with resultant cyanosis. However, it is clear that a central disturbance in the vasomotor mechanism was present in some of our patients. Unilateral flushing was noted in one patient, who had a contralateral focus of epileptiform activity secondary to a brain tumor.

Other evidences of autonomic discharge may be seen in association with any of the phenomena described previously (Table 4). Profuse sweating may occur. Other patients complain of pilomotor disturbances, and some complain of feelings of warmth or cold. One patient, who had evidences of a contralateral focus of epileptiform activity, observed paroxysmal unilateral sweating of the contralateral half of his body.

### GENITOURINARY SYMPTOMS

Five patients described symptoms suggesting involvement of the genitourinary system. Urinary incontinence is a frequent component of a generalized seizure. More rarely it occurs paroxysmally as a major manifestation of a minor seizure. Three patients were encountered in whom incontinence not associated with unconsciousness occurred as a major portion of the attack. When urinary incontinence is a major part of an attack, it may be confused with psychogenic incontinence.

CASE 9.—A 40-year-old woman complained that for the past three years she had noted episodes that she termed "wetting spells." She described an attack as follows: "It begins with a scared, frightened feeling which starts in the lower abdomen and goes right up to my nose. I then stop talking, and feel as if I freeze. I can't move, and I lose control of my bladder. This lasts for

fifteen or twenty seconds. When the episode stops, my hands tremble. I can remember what was said before the spell, and if I think hard I can remember what was said when I was in the spell. During the attack my husband says I may be flushed." Recently she had been having as many as three of these episodes in a day. Her husband had observed that sometimes the episodes were associated with slight loss of awareness and that on occasion she had dropped objects. She had never been incontinent at any other time.

Prior to our examination the patient was studied extensively elsewhere and it was concluded that the attacks were psychogenic. Because of progression of her symptoms in spite of psychiatric treatment, the patient sought other medical opinion. At the time of our study, neurologic examination and an electroencephalogram showed no abnormalities. Pneumoencephalography revealed depression of the anterior position of the left lateral ventricle by a mass. Neurosurgical exploration revealed a subcortical infiltrating oligodendroglioma of the left frontal parasagittal region. In the six months after operation, this patient has experienced fewer than five attacks.

Paroxysmal genital symptoms are rarely described by these patients. A history of symptoms related to the genitalia is difficult to obtain; the two patients from whom we obtained a history of paroxysmal genital sensations were extremely reticent about these symptoms and did not mention them at the time of their first examination. One patient described unusual sensations about her genitalia that were similar to those of a sexual orgasm. At first these symptoms occurred alone but later were invariably followed by grand mal. The electroencephalogram revealed diffuse abnormalities. Similar symptoms were described by another patient.

Case 10.—This 43-year-old man had experienced attacks for 17 years. He said they first came as a feeling of "tingling" in his testes. During these episodes he could not talk and was somewhat confused. Fifteen years ago he had had two grand-mal convulsions. Since then he had continued to have attacks of tingling paresthesia in the abductor regions of the thigh; the paresthesia sometimes involved the scrotal area. Following this, piloerection occurred along the thighs and he sometimes became unconscious. If the attacks occurred at night, he usually had a grand-mal convulsion. An electroencephalogram showed slow waves originating from a focus in the left temporal lobe. A pneumoencephalogram revealed nothing abnormal.

### RISING VISCERAL SYMPTOMS

Seventeen patients described a paroxysmal sensation usually beginning in the epigastrium and rising rapidly to the throat, at which time consciousness was lost. These sensations have been termed in the past "rising epigastric sensations."[4] We propose to term them "rising visceral sensations," inasmuch as the feeling may begin not only in the epigastrium but occasionally in the lower extremities or genitalia. It has been suggested that they are related to the gastrointestinal system, but this appears unlikely, as in our experience the symptoms are not limited to this system. The patient invariably states that the sensation appears to be in the viscera. It may be described as freezing or prickling and occasionally as a sense of rising warmth. In our experience, these attacks are most frequently associated with generalized seizures and have not been particularly useful in the localization of lesions.

Case 11.—A 50-year-old man began to have the following attacks at the age of 16 years. He stated that, "I have a feeling like electricity going up my legs and then a pressure in my belly which works up toward my throat. When it reaches the throat I lose consciousness." This sensation sometimes was repeated many times a day and frequently was not associated with any further symptoms. At times, however, the rising sensation was followed by a generalized convulsion. Results of routine laboratory and roentgenologic studies were within normal limits. An electroencephalogram revealed slow waves arising from a focus in the region of the left temporal lobe.

COMMENT

The presence of these visceral symptoms in patients who have convulsive disorders is of theoretic and therapeutic significance. The patterns of seizures in these patients indicate the presence of two principal locations of visceral representation in the cerebral cortex: (1) the frontotemporal region, which includes the anterior portion of the temporal lobe, the insula, and the posterior orbital surface of the frontal lobe, and (2) the midfrontal parasagittal region, involving the medial side of the frontal lobe. This conclusion appears to be in accord with the presently available evidence concerning the function of these regions in man. Penfield and Rasmussen [9] concluded from the effects of electric stimulation that alimentary sensory and motor representation lies in the superior bank of the sylvian fissure and the insula. Later, Penfield and Welch [10] reported epigastric sensations with stimulation of the supplemental motor region. Evidence for representation of alimentary function in the temporal region has also been presented by Daly and associates [11] and by MacLean and Arellano.[12]

In our patients the precise nature of the abdominal symptoms is not always understandable. Clearly, such phenomena as vomiting, borborygmi, involuntary defecation, or urinary incontinence are indicative of motor responses involving the viscera. However, in other patients it cannot be determined with certainty whether the symptoms are motor or sensory in character. Thus, paroxysmal pain may be caused by spasm of the intestine or it may represent a sensory phenomenon interpreted by the patient as pain in a viscus. At present, we are unable to state definitely the site of origin of the pain. In some patients it is possible that relatively prolonged epigastric distress, particularly that which may occur after the seizure, may be a manifestation of pylorospasm. In one patient dull epigastric pain persisted after the seizure; this was relieved only by vomiting. Finally, in some patients the phenomena noted would appear to be purely sensory in character. Thus, sensations such as a "caved-in feeling" or an "all-gone feeling" or the complaints of certain patients whose epigastric sensations have affective qualities may be assumed to be purely sensory in origin.

Similar evidence demonstrates the existence of cardiovascular centers in the same regions. Livingston and associates [13] noted that elevation of blood pressure occurred after stimulation of a region on the orbital surface of the frontal lobe which overlapped but was not identical with that from which arrest of respiration was obtained. Chapman and co-workers [14] observed elevation of blood pressure after stimulation of the tips of the temporal lobes in one patient. Pool and Ransohoff [15] noted elevation of blood pressure and increase or decrease in both cardiac and respiratory rates after stimulation of the anterior portion of the gyrus cinguli. Changes in cardiac rate have also been reported by Penfield and Welch. Vasomotor responses manifested by flushing or pallor have been noted by Daly and co-workers and by MacLean and Arellano.

In this series of patients we have noted both cardiac acceleration and deceleration. In no instance have we been fortunate enough to measure the patient's blood pressure during an attack. However, in an attack witnessed in one patient during the recording of the electroencephalogram it was clear that a profound decrease in blood pressure had taken place, associated with loss of consciousness and changes

in the electroencephalogram consistent with cortical anoxia. Flushing and pallor have been noted in this series as common manifestations of changes in vasomotor tone.

Disturbances in respiratory control also have been noted after stimulation of the supplemental motor region.[10] Kaada and Jasper [16] have reported inhibition of respiration in the expiratory phase after stimulation of the temporal pole, insula, the hippocampal gyrus, and the gyrus limbicus. Livingston and associates noted the same effect with stimulation of the orbital surface of the frontal lobe. Inhibition of respiration after stimulation of the region of the uncus was described by Liberson and co-workers.[17]

Evidence of autonomic responses after stimulation of the cerebral cortex in animals is to be found in numerous articles in the literature pertaining to physiology, to which we shall make only brief reference. Babkin and associates * reported that stimulation of the anterior portion of the gyrus cinguli and of the "insular-orbital" region inhibited spontaneous contractions of the pyloric antrum, while, conversely, ablation of the gyrus cinguli on both sides increased the rate of contraction. On rare occasions after stimulation, an increase in the rate of spontaneous contractions was observed. It is of interest that on no occasion did these authors note vomiting.

Numerous reports described cardiovascular and respiratory phenomena after stimulation. In 1894, Spencer [21] reported respiratory irregularities after stimulation of the orbitotemporal region. MacLean [22] described autonomic phenomena, such as lacrimation, salivation, pupillary changes, piloerection, and cardiac slowing, together with acceleration or inhibition of respiration, after stimulation of the frontotemporal portion of the limbic system of the cat. Babkin and Kite [23] reported inhibition of rhythmic fluctuations in blood pressure produced by stimulation of the orbital regions of the frontal lobe. Changes in respiratory rate, blood pressure, and cutaneous temperature may be seen after stimulation of the orbital surface.[24] Similar effects have been described by Kaada and associates.[25] Ward [26] has reviewed similar effects that may be noted after stimulation of the gyrus cinguli.

The anatomic substrates for these physiologic phenomena are at present not entirely clear. Presumably the projections from those cortical regions that serve as autonomic centers are to lower centers known to exist in the hypothalamus and lower part of the brain stem. Evidence exists suggesting that the orbitotemporal region has extensive corticocortical connections within itself. By means of neuronography with strychnine, Pribram and his associates [27] have demonstrated intimate connections among the orbital surfaces of the frontal lobe, insula, temporal pole, and the periamygdaloid and entorhinal regions. Similar conclusions also have been reached on the basis of studies of degeneration.[28] Recently evidence has been offered that the tip of the temporal lobe and the amygdaloid complex project to the ventromedial hypothalamic nuclei, a region from which it is known that autonomic phenomena can be produced by stimulation.[28] This same region of the hypothalamus is also known to receive fibers from Areas 6 and 13 in the frontal lobes. The efferent connections in the region of the gyrus cinguli have been discussed

* References 18-20.

by Ward. Similar conclusions regarding the projection of the temporal region on the hypothalamus have been reached on the basis of studies of evoked potentials by Marsan and Stoll.[29]

Finally, it is of interest that evidence exists implicating these same general regions in emotional behavior, although at present the precise relationship is not clear.† It has long been recogfinized that disturbances in affect may be associated with seizures originating in the temporal region. These alterations of mood may be paroxysmal and clearly associated with the attack, or they may occur as non-paroxysmal phenomena. This relationship has been discussed in a previous study from this clinic.[32]

The diagnosis of visceral epilepsy is rarely difficult if an adequate history is obtained and if the physician is cognizant of the syndrome. The episodes are brief, stereotyped, and paroxysmal. They often are associated with disturbances in consciousness of which the patient is not aware. Visceral symptoms may precede a major convulsive seizure. Careful interrogation of relatives frequently reveals that the attack is accompanied by motor movements, respiratory arrest, or vasomotor disturbances. Paroxysmal psychopathologic symptoms, such as hallucinations, perceptual illusions, automatisms, and disturbances of affect, are often associated with the visceral symptoms. These concomitant paroxysmal phenomena suggest that the responsible lesion probably is cerebral. Neurologic examination frequently reveals other evidence of cerebral disease; the electroencephalogram is particularly helpful in diagnosis. In some patients it is possible to precipitate an attack and so confirm the diagnosis. The visceral symptoms are not aggravated by those factors which tend to precipitate intrinsic visceral disease, nor are they benefited by treatment intended to alleviate visceral disease. However, they frequently do respond to administration of anticonvulsant drugs.

The usual differential diagnosis includes primary visceral disease and psychosomatic disorders. A diagnosis of primary visceral disease is rarely considered, apparently because of the bizarre and atypical symptoms observed in visceral epilepsy. Concepts in medicine change, and today a syndrome that appears bizarre is frequently diagnosed as psychosomatic. The presence of paroxysmal psychopathologic symptoms apparently may confirm an incorrect psychiatric diagnosis. The understandable anxiety of the patient about bizarre and uncontrollable symptoms, that are perhaps not understood by the physician either, may add to the confusion. Correct diagnosis depends on recognition of the paroxysmal occurrence of the symptoms and their inappropriateness to the total situation, together with association of other symptoms and findings suggestive of cerebral involvement. Jackson [33] stated that "the great thing as to the diagnosis of epilepsy is not the 'quantity' of the symptoms, nor the severity of the fits, but paroxysmalness."

Management of visceral epilepsy is aimed when possible at localization, identification, and eradication of the focal cerebral lesion causing the disorder. Brain tumor must be considered in differential diagnosis in each patient; this is particularly pertinent if the attacks begin after adolescence. If surgical extirpation of the lesion is not possible, conservative therapy is indicated. This includes the usual hygienic, psychologic, and anticonvulsant measures that one of us (Bailey [34]) has discussed elsewhere.

† References 30 and 31.

SUMMARY

A study was made of 100 patients who had paroxysmal visceral symptoms occurring either as an aura to an epileptic attack or as the attack itself. The diagnosis of epilepsy was confirmed by evidence in the histories, by complete neurologic studies, and, in certain instances, by observation of attacks.

Localized cerebral lesions responsible for the symptoms were found in 83 cases. The temporal lobes or the frontal parasagittal regions were the site of these discharging foci. This study supports other physiologic evidence that these zones are important in the control of visceral function.

Gastrointestinal, cardiorespiratory, genitourinary, and rising visceral symptoms were observed as epileptic attacks. The bizarre nature of the complaints frequently led to a diagnosis of psychiatric disease or, rarely, to a diagnosis of localized visceral disease. Visceral epilepsy is a form of focal epilepsy that can be recognized by the paroxysmal occurrence of the symptoms, their unrelatedness to visceral pathologic changes, and the association of other symptoms and findings suggestive of cerebral disease.

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# AMYLOIDOSIS

## Report of Three Cases with Some Considerations as to Etiology and Pathogenesis

ALBERT JACKSON, M.D.
WADSWORTH, KAN.

ROKITANSKY [1] first described a disease entity in which many organs exhibited a firm waxy substance. Later Virchow [2] noted that this substance stained blue-black with iodine and showed some similarity to starch. He therefore called this substance "amyloid" and the disease entity "amyloidosis." Wilks [3] was the first to note that this disease followed chronic suppurative conditions.

It is customary to classify amyloidosis as (1) primary amyloidosis, also called systemic or focal amyloidosis, the etiology of which is unknown; (2) secondary amyloidosis, in which the disease is an end-result of other chronic diseases, such as ulcerative colitis, tuberculosis, bronchiectasis, osteomyelitis, or cancer, and (3) amyloidosis following multiple myeloma.

Amyloidosis, either primary or secondary, is still a relatively rare disease. Approximately 80 cases of primary amyloidosis have been reported to date.[4]

In primary amyloidosis the organs usually affected are the myocardium and skeletal muscles.[5] Other organs, such as the spleen, liver, adrenals, and kidneys, which are usually affected in secondary amyloidosis, are also involved in primary amyloidosis but to a minor degree. Nevertheless, primary systemic amyloidosis of the alimentary tract [6]; larynx, trachea, and bronchi [7]; lungs [8]; bone marrow [9]; spleen *; liver,† and kidneys ‡ has been reported. In many cases of primary amyloidosis extensive involvement of the liver, spleen, and kidneys has been reported similar to that usually encountered in secondary amyloidosis.§ In secondary amyloidosis, on the other hand, the heart is involved much more frequently than was originally thought. Dahlin [22] reported about 30 cases of secondary amyloidosis, and he states that after careful study amyloid was found in organs which ordinarily are not considered to be affected. He states that with special stains amyloidosis is frequently found in organs which are usually considered to be infiltrated only in primary amyloidosis. For instance, in 80% of his cases of "secondary" amyloidosis, amyloid deposits were found in the heart in the reticulum between the muscle fibers and the capillaries. This percentage was so high because the heart was stained with methylene, the only stain which revealed amyloidosis.

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From the Veterans Administration Center (Dr. Jackson, Cardiologist).

* References 10, 11, and 12.

† References 4 and 13-17.

‡ References 18 to 19.

§ References 12, 13, 14, 18, 20, 21, and 41.

The kidneys are supposed to be almost always involved in secondary amyloidosis. Yet in Dahlin's series the kidneys showed amyloidosis in only 28 of the 30 cases of secondary amyloidosis studied.

It can, therefore, be stated that, as far as the morphology is concerned, the difference between so-called primary and secondary amyloidosis is of a quantitative rather than of a qualitative nature. In my opinion this does not justify a grouping into separate entities.

Wilks [8] was the first to report amyloidosis following rheumatic disease. This association is rather infrequently found. Rheumatoid arthritis occasionally causes secondary amyloidosis.[23] In 1948 Unger [24] reported 10 cases of rheumatoid arthritis followed by amyloidosis and collected approximately 40 cases from the literature.

Amyloidosis following rheumatic fever is even more rare.‖ Dillon [12] reported a case of rheumatic fever with amyloidosis under the caption of primary amyloidosis.

Amyloidosis in two cases of rheumatoid arthritis and in one case of rheumatic fever were recently observed at this hospital. Because of the relative rarity of these conditions, and because of the etiopathologic and therapeutic implications, these cases are reported briefly.

CASE 1 (W. H. 82 156).—The patient was admitted to this hospital in 1939 because of atrophic arthritis. X-rays showed the entire spine to be involved in a severe type of arthritis characterized by calcification of the spinous ligament and bridging along the lateral and anterior margins of the bodies of the vertebrae. The left hip showed narrowing of the joint space, considerable erosion of the superior margin of the acetabulum, and atrophy of the head of the femur. The right knee showed arthritis.

He was readmitted in August, 1940, and x-rays showed that the hips and the sacroiliac and lumbosacral joints, together with the entire thoracic and lumbar spine, demonstrated further progression of the disease.

On his third and last admission the patient was completely bedfast and he had recently developed shortness of breath.

Physical examination revealed a pale fairly well-developed and well-nourished white man, aged 52. His neck was fixed, and he was unable to open his mouth completely. Eyegrounds showed increased tortuosity of the arteries, with increase in light reflection and notching of the AV crossings. There was a large perforation of the nasal septum. The expansion of the chest was limited, and there were moist rales heard in both lung fields. The blood pressure was 180/118. The abdomen was slightly protuberant. There was fixation of the neck, spine, knees, and ankles due to rheumatoid arthritis. The left knee could be moved only slightly. There was a fair range of movement in the arms, elbows, and hands, although the patient was unable to raise his arms above his head.

Laboratory examinations revealed an RBC count of 3,000,000; WBC count of 13,000; 78% neutrophils. Urinalysis showed a 4+ albumin. NPN was 57 mg. per 100 cc. Creatinine was 4.1 mg. per 100 cc. P.S.P. test showed a trace of dye excreted. Total protein was 5.5 gm., albumin 2.0 gm., globulin 3.5 gm., and A/G ratio 0.6.

X-ray of the chest showed left hydrothorax and cardiac enlargement.

*Hospital Course.*—The patient was treated with digitalis, diuretics, and low-salt diet. He continued to show a downhill course and died 17 days after admission, Oct. 21, 1949.

*Postmortem Examination.*—Gross Findings: Gross pathological findings revealed the right chest to contain 900 cc., and the left chest 1,200 cc., of slightly cloudy fluid. The parietal pericardium was found to be adherent to the visceral pericardium over the apex and posterior aspect of the heart. The aorta showed a very minimal amount of arteriosclerosis. The spleen was not remarkable. The liver showed passive congestion. The right kidney weighed 100 gm. and the left 130 gm. They were soft and pale. The capsule stripped with some difficulty. The surface

‖ References 25 and 26.

was studded with multiple yellow spots measuring up to 8 mm. in diameter. The cortices and the medullae were pale. The medullary rays were indistinct. The corticomedullary junction was poorly defined.

Microscopic Examination: The lungs showed occasional small areas of amyloid infiltration in the walls of the alveoli and also some bronchopneumonia.

In the heart were noted occasional small areas of amyloid infiltration in the interstitial tissue of the media and adventitia of the blood vessels. The liver showed passive congestion. The spleen was characterized by extensive deposition of amyloid of the focal type, with replacement of all follicles. The central arteries contained amyloid deposits in the media and adventitia. The pancreas showed spotty deposition of amyloid. There was atrophy of the cortical tissue of the adrenals with marked deposition of amyloid. The kidneys showed marked severe infiltration of the glomeruli, with obliteration of the capillaries in almost all the glomeruli examined. There was marked perivascular infiltration with amyloid, and there was widespread tubular atrophy, with an increase of the interstitial and intertubular connective tissue.

*Final Diagnosis.*—Rheumatoid arthritis; diffuse secondary amyloidosis involving the heart, adrenals, spleen, liver, and kidneys; bronchopneumonia; mild passive congestion of the liver; pericarditis.

CASE 2.—G. J., 88 998, a 39-year-old white man, had been suffering from bronchial asthma and cardiac distress for the past seven or eight years. In 1949 he had been in this hospital, at which time a diagnosis of bronchial asthma and rheumatic valvular heart disease with mitral stenosis was made. He improved on digitalis and was discharged at that time completely compensated.

On June 21, 1950, the patient's wife noticed that he was dyspneic and cyanotic and he was admitted to the hospital moribund. He developed pulmonary edema and died a few hours after admission.

*Postmortem Examination.*—Gross Findings: Each pleural cavity contained 300 cc. of straw-colored fluid. There were no adhesions. The pericardial sac contained 50 cc. of clear straw-colored fluid. The lungs were not remarkable. The heart weighed 440 gm. There were several small irregularly outlined white fibrotic plaques beneath the endocardium of the lateral wall of the left ventricle. Sections of that region showed small fibrotic scars. The mitral valve showed the classical "fish mouth" deformity and was markedly thickened. A few firm fibrous vegetations were present. The aortic valve likewise showed fusions of two of the cusps over a distance of 1.3 cm. Along the free border there were also small multiple vegetations present. The coronary arteries showed a moderately severe degree of atheromatous thickening. The heart showed a few atheromatous plaques. The duodenum contained two small healed peptic ulcers. The remainder of the postmortem examination was not remarkable.

Microscopic Examination: Sections through the myocardium showed areas replaced by hyalinized fibrous tissue. Section through the mitral valve showed marked thickening and marked hyalinized connective tissue. No structures suggestive of Aschoff bodies were seen. The spleen showed a moderate degree of amyloid infiltration of the lymph nodes.

*Final Diagnoses.*—Coronary sclerosis complicated by healed myocardial infarcts; mitral stenosis; amyloid degeneration of the spleen; advanced chronic passive congestion of the viscera; healed duodenal ulcers.

CASE 3 (M. J. 40 933).—This patient was admitted to the hospital for the first time in 1940, at which time a diagnosis of multiple rheumatoid arthritis was made.

He was readmitted to the hospital in 1942 because of progressive stiffness of the joints and because of increased helplessness.

*Physical Examination.*—Examination revealed a fairly well-developed and well-nourished 52-year-old white man. His teeth had been removed and were replaced by artificial dentures. The blood pressure was 170/90. There were no murmurs, no trills, and no arrhythmias. The lungs were clear. The right knee joint was enlarged. The flexion and extension of the knees was limited. The elbows were held in a slight degree of flexion, with restriction of movement. The patient was unable to straighten out his fingers. The interphalangeal, metacarpal, and phalangeal articulations, as well as the wrists, were swollen and enlarged. The range of motion of both shoulders was restricted. There was crepitation of all involved joints. No involvement of the hips was found.

*Hospital Course.*—Throughout the almost 10 years of hospitalization the patient showed remissions and exacerbations. He received very extensive symptomatic and supportive treatment. He was also treated with gold and later with corticotropin (ACTH), without improvement. His general condition remained stationary until 1951, at which time he became decompensated and died, in December, 1951.

*Laboratory Examinations.*—An enormous amount of laboratory work was done during this patient's hospital stay, and only the most significant findings are reported. On admission his blood cell count, urinalysis, and chemistry were normal. On Sept. 14, 1951, the cephalin-flocculation test was 3+. Total protein was 5.5 gm., albumin was 2.6 gm., globulin 2.9 gm., and A/G ratio 0.9. Blood cell count on Aug. 30, 1951, was 4,060,000, with 11% hemoglobin. NPN on Aug. 5, 1951, was 47 mg. Urinalysis on Aug. 8, 1951, showed a trace of albumin, with 6 WBC per high-power field. Later urinalysis showed a 3 to 4+ albumin, with occasional granular casts. Blood cell count began to drop and went down to 2,950,000, with 55% hemoglobin. Sedimentation rate was always elevated. Serologic tests in 1942 showed a 2+ Wassermann and a 1+ Kahn reaction. In 1951 results of serologic tests were doubtful.

*Postmortem Examination.*—Gross Findings: The body was that of an emaciated white man with severe arthritic changes of the hands, knees, feet, and elbows—in other words, of all joints of his body. There was a marked fixation of the knees in a flexed position. There was 700 cc. of thick grayish-brown pus in the left thoracic cavity. The pericardial sac contained 100 cc. of turbid reddish-brown fluid. The lungs showed pulmonary edema. There were adhesions of the left lung. The heart weighed 550 gm. There was thickening of the left ventricle. The aorta was dilated and showed sclerotic changes. The coronary vessels were thickened, hard, and sclerotic. The lumen of the coronary vessels was narrowed. The posterior wall of the left ventricle showed small areas of fibrosis. The spleen weighed 220 gm. The liver weighed 2,200 gm. The stomach contained an ulcer of the lesser curvature, which had perforated.

Microscopic Examination: Sections through the heart showed irregular interstitial fibrosis. The lungs contained an early bronchopneumonic exudation. In the spleen there was amyloid infiltration of the Malpighian bodies. The kidneys were characterized by moderately advanced chronic glomerulonephritis, with many glomeruli completely hyalinized; they also showed amyloid infiltration. On the lesser curvature of the stomach there was an ulcer which had perforated. Sections of the adrenals were not remarkable.

*Final Diagnoses.*—Rheumatoid arthritis; bilateral bronchopneumonia; empyema of the left chest; perforated gastric ulcer; generalized arteriosclerosis; coronary sclerosis; chronic glomerulonephritis; amyloid infiltration of the spleen and kidneys.

## COMMENT

Nothing definite is known about the etiology of amyloidosis. It was discovered a long time ago, however, that amyloidosis is in some way related to protein. Kuczynski [27] fed mice with casein-rich food or injected casein preparations into mice and produced amyloidosis. Snapper [28] found that there is relatively little amyloidosis in the Orient, where the diet is low in protein. In King's [10] case the patient had been taking large amounts of milk and cheese for three years prior to the development of amyloidosis of the spleen. It is also possible to produce experimental amyloidosis by means of repeated staphylococcus infections and by means of injection of foreign proteins (Dick,[29] Ecklund,[30] Jaffe [31]).

It has been noted that hyperglobulinemia is not infrequently encountered in experimental amyloidosis (Reimann [32]). Hyperglobulinemia is also found frequently in primary and secondary amyloidosis, mostly due to a relative increase in the gamma globulin fraction. Jensen [34] reported amyloidosis associated with chronic ulcerative colitis, and Cohen [35] reported amyloidosis associated with regional enteritis with a reversal of the albumin/globulin ratio.

A reversal of the albumin/globulin ratio has also been found in primary systemic amyloidosis, as reported by Dahlin,[4] Eisen,[5] Couter,[33] Dillon,[12] Zetzel,[14] Findley,[20]

Iverson,[36] Lindsay,[37] and Reimann.[32] Amyloid is composed of polysaccharides similar to chondroitin sulphuric acid, which is known to be a component of collagenous tissue (Hass [38]). It differs only in that a different kind of protein is precipitated (Ehrich [39]).

That amyloid is formed by perverted fibroblastic activity is suggested by Mallory.[40] Jones and Frazier [41] believe that amyloidosis is an alteration of a mucopolysaccharide-reticulum response. According to these authors, the proteins are precipitated by a reaction of the circulating antigen with the antibody. They think that amyloid could be a combination of mucopolysaccharides with a variety of proteins which are involved in the antigen-antibody reaction. Likewise, Ehrich [39] believes that amyloid deposition may be due to faulty production of a pathological protein either by normal or by abnormal plasma cells and that amyloid may be a precipitate of protein with mucopolysaccharides. In collagen diseases the blood shows an increase in the mucopolysaccharides and gamma globulins. The gamma globulins are produced by the mesenchymal cells, and therefore in conditions causing mesenchymal reaction there is an elevation of gamma globulins (Popper [42]).

Hyperglobulinemia with reversal of the albumin/globulin ratio is classic in multiple myeloma. The sequence of events in amyloidosis following multiple myeloma therefore seems to be clear: There is an abnormal production of plasma cells, with faulty production of protein and precipitation of these proteins in the collagen tissue. It is therefore quite possible, as Apitz ¶ postulates, that every case of primary amyloidosis is associated with plasma cell proliferation and that primary amyloidosis is either an unrecognized or a burned-out case of plasma cell proliferation. Up to date there have been only about 80 cases of primary amyloidosis reported. Many cases were not recognized during the patient's life, and no bone marrow studies were performed. And even negative plasma cell findings in the bone marrow could mean that the process has subsided and that we are dealing with a burned-out case.

As far as diseases leading to secondary amyloidosis are concerned, few, if any, studies for plasma cell proliferation have been performed even when the possibility of secondary amyloidosis has been considered.

It is known that corticotropin and cortisone have a profound action on the ground substance. They inhibit fibroblastic proliferation and collagen fiber formation, decrease antibody formation, reduce plasma cells and gamma globulin, and diminish the permeability of the connective tissue.

Corticotropin and cortisone are helpful in all conditions responsible for the ultimate production of so-called secondary amyloidosis.

That corticotropin and cortisone have been successfully used in rheumatic fever, rheumatoid arthritis, regional enteritis, and ulcerative colitis needs no further amplification. Corticotropin and cortisone have also been tried in multiple myeloma.

Corticotropin and cortisone are contraindicated in tuberculosis only because they cause a diminution of the inflammatory reaction, less granulation, depression of collagen formation, and interference with the immune response. Corticotropin and cortisone therefore mask the progression of the underlying tuberculous process. Corticotropin and cortisone are not bacteriocidal or bacteriostatic. As Ebert [43] states: "It is possible to reduce with cortisone the apparently useless inflammatory response in diseases such as rheumatoid arthritis."

¶ Apitz, K.: Cited by Ehrich.[39]

Rheumatoid arthritis and rheumatic fever are collagen diseases. There is no suppuration in rheumatoid arthritis and in rheumatic fever. Hyperglobulinemia is frequently present in rheumatoid arthritis (Archer [44]). Rheumatic disease can terminate in amyloidosis. It is therefore possible that in rheumatic disease an imbalance of the albumin/globulin ratio causes precipitation of the circulating protein, its deposition into the sensitized collagen tissue with ultimate transformation into amyloid.

The same agent which causes rheumatic disease can also cause amyloidosis, either contemporaneously or subsequently. Rheumatoid arthritis and rheumatic fever are usually evident and easily diagnosable diseases—amyloidosis is not. It could be that both rheumatic disease and amyloidosis develop at the same time in the patient; one is easily seen and diagnosed, the other is occult and not diagnosed but nevertheless present, to be discovered only accidentally at postmortem examination. Or, rheumatic disease might be an early manifestation and amyloidosis a late manifestation of the same stimulus that causes hyperirritability of the collagen.

There are many stimuli capable of causing collagen disease. Concerning rheumatic fever, for instance, Bland and Jones [45] state that it might be due not only to streptococcic sore throat but "also to trauma, surgical operation, exposure to cold, and to a non-specific protein shock reaction. It is a hyperirritability to many stimuli."

A multitude of stimuli can also be responsible for causation of amyloidosis.

Rheumatic fever and rheumatoid arthritis—admittedly collagen diseases—form the etiological link between so-called "primary amyloidosis," of unknown etiology, and so-called "secondary amyloidosis," in which one collegen disease is followed by another collegen disease or at least by another disease of the ground substance with very similar morphologic and blood chemistry findings.

A multitude of stimuli can cause irritation of the ground substance, to which it responds with a multitude of morphologically and chemically similar but clinically protean manifestations, from serum sickness, rheumatic fever, rheumatoid arthritis, dermatomyositis, and scleroderma to sarcoidosis and amyloidosis.

Waksman's statement concerning the etiology of rheumatic fever can be amplified to include also other diseases like amyloidosis. Waksman states [46]:

> What process is set in motion by these various events is not known; it may be the adaptation syndrome of Selye, a non-specific allergic response, an increasing type of antibodies against some constituent of connective tissue or even the reactivation of a latent virus infection.

There is no definite answer to the question: Which comes first—reversal of the albumin/globulin ratio followed by precipitation of the circulating protein, or hypersensitization of the collagen tissue followed by precipitation of protein?

A long time ago Leupold [47] postulated that amyloidosis was caused by acidification of the connective tissue with an increase of the chondroitin sulphuric acid which caused precipitation of abnormal circulating proteins. He thought that the product of protein disintegration underwent fermentative liquefaction, with deposition of amyloid in the collagen tissues.

Dick [29] has found that hyperproteinemia diminishes when amyloid develops. This suggests to him that the protein is deposited in the tissues.

Ehrich [39] states that "the injury in the connective tissue is associated with, or preceded by, an elevation of the gamma globulin."

The fact that hyperproteinemia with hyperglobulinemia has been reported in cases of amyloidosis without liver or kidney function impairment would favor the first hypothesis (Dahlin [4] thinks that the reversal of the albumin/globulin ratio found in his cases of primary systemic amyloidosis was probably not due to renal disease, because the total serum proteins were not reduced).

Later in the course of the disease there might be a vicious circle; amyloid deposition in the liver, kidneys, or spleen, for instance, interfering with the normal function of these organs and causing a further reversal of the albumin/globulin ratio, which in turn causes further precipitation of protein into the sensitized collagen tissue. It should be mentioned that disturbance of hepatic function because of amyloidosis is rare and that jaundice is exceptional in amyloidosis.#

If there is no difference between primary and secondary amyloidosis as far as the morphology is concerned, there is no justifiable differentiation as far as the etiology and pathogenesis are concerned.

## SUMMARY AND CONCLUSIONS

Three cases of "secondary amyloidosis" after rheumatoid arthritis and rheumatic fever are presented.

There is no essential difference between the distribution of amyloid in "primary" and "secondary" amyloidosis. The difference is more of a quantitative than of a qualitative nature.

In the disease entities eventually leading to "secondary amyloidosis" there is an imbalance of the albumin/globulin protein ratio, which is probably responsible for the deposition of protein in the tissues.

In "primary amyloidosis" there is, likewise, frequently an imbalance of the albumin/globulin ratio.

The similarity between amyloidosis and collagen diseases is reviewed. It is accepted that collagen disease is a hypersensitivity disease. Likewise, "secondary amyloidosis" is a disease of the collagen system due to hypersensitivity. It can be assumed that "primary amyloidosis" is also a hypersensitivity disease, due to either plasma cell proliferation (present or burned-out) or caused by agents similar to those causing rheumatic fever and rheumatoid arthritis.

Amyloidosis (either "primary" or "secondary") is therefore not considered to be a separate entity but a manifestation of the hypersensitivity disease.

Corticotropin (ACTH) and cortisone are beneficial in conditions leading to "secondary amyloidosis," including multiple myeloma (tuberculosis excepted). Corticotropin therapy also seems to be justified in "primary amyloidosis."

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# TREATMENT OF ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS WITH CORTICOTROPIN AND CORTISONE

LOUIS J. SOFFER, M.D.
SAMUEL K. ELSTER, M.D.
AND
DAVID J. HAMERMAN, M.D.
NEW YORK

THIS REPORT deals with the results of a prolonged follow-up study of 32 patients with acute disseminated lupus erythematosus treated with corticotropin and cortisone. Our initial study commenced 40 months ago, and in our earlier

TABLE 1.—*Age, Sex, and Race Distribution of Patients with Acute Disseminated Lupus Erythematosus*

| | Patients, No. |
|---|---|
| Sex | |
| Male | 6 |
| Female | 26 |
| Age, Yr. | |
| 0-10 | 0 |
| 11-20 | 7 |
| 21-30 | 11 |
| 31-40 | 6 |
| 41-50 | 3 |
| 51-60 | 5 |
| Race | |
| White | 27 |
| Negro | 3 |
| Other * | 2 |

* Mexican, Puerto Rican.

reports we described the results obtained in a limited number of patients with these therapeutic agents.*

Our series of patients includes 26 females and 6 males, and the ages of the patients varied from 11 to 60 years (Table 1). The largest incidence of the disease occurred during the second, third, and fourth decades, but almost no age group is immune to the possible onset of this illness. All patients included in the investigation were admitted to the general medical wards of The Mount Sinai Hospital and were followed by the same group of investigators throughout the period of study, both while the patients were in the hospital and, when they were subsequently dis-

From the Endocrine Laboratory and Clinic of the Department of Medicine, The Mount Sinai Hospital.

* References 1-5.

charged, in the clinic. The hospital stay varied from one to nine months, and the patients were then discharged to a special out-patient department, where they were seen at weekly or biweekly intervals thereafter.

TABLE 2.—*Duration of Illness Prior to Treatment with Corticotropin (ACTH) or Cortisone in 32 Patients with Acute Disseminated Lupus Erythematosus*

| Years | Patients, No. |
|---|---|
| 0-½ | 8 |
| ½-1 | 11 |
| 1-2 | 5 |
| 2-3 | 1 |
| 3-4 | 3 |
| 4-5 | 1 |
| More than 5 | 3 |

TABLE 3.—*Initial Symptom with Onset of Acute Disseminated Lupus Erythematosus*

| Symptom | Patients, No. |
|---|---|
| Arthralgia | 18 |
| Rash | 5 |
| Arthritis | 2 |
| Fever | 2 |
| Hoarseness and lymphadenopathy | 1 |
| Nonspecific weakness | 1 |
| Alopecia | 1 |
| Pleuritic pain | 1 |
| Weight loss | 1 |

TABLE 4.—*Incidence of Symptoms in 32 Patients with Acute Disseminated Lupus Erythematosus*

| Symptom | Patients | |
|---|---|---|
| | No. | % |
| Fever | 31 | 97 |
| Arthralgia | 30 | 94 |
| Weight loss | 24 | 75 |
| Rash | 23 | 72 |
| Arthritis | 19 | 59 |
| Chills or chilliness | 16 | 50 |
| Chest pain | 13 | 40 |
| Abdominal pain | 7 | 22 |
| Alopecia | 6 | 19 |
| Lymphadenopathy | 6 | 19 |
| Bleeding tendency | 4 | 13 |
| Convulsions | 8 | 25 |

## CLINICAL MANIFESTATIONS

In Table 2 is listed the duration of illness prior to treatment with corticotropin (ACTH) or cortisone. Most of the patients had been ill for six months to two years before admission to this study. Three patients, however, had been ill with disseminated lupus erythematosus for more than five years before they were treated with either the adrenal steroids or with corticotropin. During this pretreatment period most of the patients had had one or more spontaneous remissions, lasting from two weeks to many months.

In Tables 3, 4, and 5 are listed the various signs and symptoms exhibited by the patients during the course of the illness. Acute disseminated lupus erythematosus is a disease with protean manifestations. More than half the patients complained of arthralgias or arthritis as the initial symptom of the illness, and in two instances arthralgias occurred for two years prior to the development of more significant evidence of the disease. At some time during the course of the disease almost all patients complained of joint pains, and in more than 40% actual joint abnormalities were demonstrable on physical and roentgenological examination. Fever occurred in 97% of the patients and varied from mildly febrile episodes to instances in which the temperature reached 105.5 F. The characteristic facial erup-

TABLE 5.—*Incidence of Physical Signs in 32 Patients with Acute Disseminated Lupus Erythematosus*

| Physical Sign | | Patients | |
|---|---|---|---|
| | | No. | % |
| Lymphadenopathy | | 23 | 72 |
| Rash | | 23 | 72 |
| Mucous membrane lesions | | 16 | 50 |
| Hepatomegaly | | 14 | 44 |
| Joint abnormalities | | 14 | 44 |
| Cardiac abnormalities, total | | 14 | 44 |
| Hypertension | 3 | 9 | |
| Gallop rhythm | 3 | 9 | |
| Pericardial friction rub | 3 | 9 | |
| Pericardial effusion | 3 | 9 | |
| Significant murmur | 2 | 7 | |
| Pulmonary abnormalities, total | | 13 | 41 |
| Pleural friction rub | 3 | 9 | |
| Psychiatric abnormalities | | 10 | 31 |
| Finger tip skin lesions | | 8 | 25 |
| Edema | | 7 | 22 |
| Splenomegaly | | 7 | 22 |
| Fundal abnormalities | | 6 | 19 |
| Neurologic abnormalities | | 3 | 9 |

tion was seen in three-quarters of the patients, and half the patients had the typical shallow ulcerated mucous membrane lesions. Both the skin rash and the mucous membrane lesion not infrequently occurred for the first time late in the course of the illness. Some form of cardiovascular abnormality, such as hypertension or gallop rhythm or pericarditis, with or without effusion, or the presence of a significant murmur occurred in over 40% of the patients. The presence of hypertension in the untreated patient was almost always associated with the presence of significant renal damage. Enlargement of the liver and a palpable spleen were observed in 44% and 22% of the patients, respectively. A diffuse lymphadenopathy occurred commonly. The nodes were generally discrete, moderately enlarged, and nontender. Eyeground changes, such as segmentation of the blood vessels, small hemorrhages, and exudates, were seen in 20% of the patients. Almost one-third of our series showed some evidence of an organic mental syndrome prior to treatment. Whether the psychiatric manifestations were the result of the febrile state or represented actual disease involvement of the intracranial vessels is, of course, difficult to know.

### LABORATORY DATA

The presence of a normal or reduced total white blood cell count is the usual finding in patients with acute disseminated lupus erythematosus (Table 6). The presence of a leucocytosis in patients with this illness should raise the suspicion of the existence of a complicating process. In 22 of our 32 patients the total white

TABLE 6.—*Hematologic Data in 32 Patients with Acute Disseminated Lupus Erythematosus*

| | Patients, No. |
|---|---|
| White blood cell count, cells/cu. mm. | |
| 1000- 3000 | 5 |
| 3100- 5000 | 17 |
| 5100- 9000 | 7 |
| 9100-13000 | 3 |
| Hemoglobin,* gm./100 cc. | |
| 5.0- 7.0 | 4 |
| 7.1- 9.0 | 11 |
| 9.1-11.0 | 7 |
| 11.1-13.0 | 9 |
| Coombs' Test | |
| Number of observations | 8 |
| Positive Coombs' test | 4 |
| Clinical hemolytic syndrome | 2 |

* 31 observations.

TABLE 7.—*Laboratory Data in 32 Patients with Acute Disseminated Lupus Erythematosus*

| Laboratory Test | Patients | |
|---|---|---|
| | No. | % |
| Positive L. E. test | 32 | 100 |
| Elevated sedimentation rate, > 25 mm./hr. | 29 | 90 |
| Hyperglobulinemia (globulin > 3.5 gm./100 cc.) | 26 | 81 |
| WBC < 5,000/cu. mm. | 22 | 69 |
| Hemoglobin < 10 gm./100 cc. | 19 | 59 |
| Abnormal EEG | 7* | 54* |
| Urine | | |
| Sediment, occasional to many RBC | 17 | 53 |
| Albumin, 1+ or more | 16 | 50 |
| Abnormal chest x-ray | 12 | 38 |
| Positive serologic test for syphilis | 12 | 38 |
| Azotemia (BUN > 20 mg./100 cc.) | 10 | 31 |
| Abnormal ECG | 8 | 25 |
| Thrombocytopenia (thrombocytes < 100,000/cu. mm.) | 2 | 6 |

* Only 13 observations.

blood cell count was 5,000 per cubic millimeter or less. In only three instances did the count vary from 9,000 to 13,000. Some degree of anemia is almost always present, and in four instances the anemia was quite profound. The anemia is usually of the normochromic normocytic type. A positive Coombs test was seen in four patients, and two of this group showed a definite hemolytic anemia. Dubois † recently described three instances of acute disseminated lupus erythematosus in which the presenting syndrome was that of an acquired hemolytic anemia. A posi-

† References 6 and 7.

tive Coombs reaction was present in all three of these patients. Two additional patients in our group showed a severe thrombocytopenia (Table 7), although modest reductions in platelet numbers were not infrequently encountered. Of the two patients with severe thrombocytopenia, splenectomy was performed for one because it was believed that her condition represented an instance of primary thrombocytopenic purpura. Following the removal of the spleen the hemorrhagic tendency promptly subsided and the peripheral platelet counts attained normal levels. Microscopic examination of the excised spleen revealed changes consistent with disseminated lupus erythematosus. Later this patient developed the characteristic manifestations of this disease and repeated peripheral blood studies now showed the presence of the typical L. E. cells.

L. E. cells were found in the peripheral blood of all 32 patients with disseminated lupus reported in this series. In our experience, the L. E. cell is found readily in the peripheral blood and a search for its presence in the sternal bone marrow is generally unnecessary. An elevation in the sedimentation rate occurred in almost all instances, and a hyperglobulinemia was present in slightly over 80% of the patients. More than half the patients showed some renal function abnormalities, such as the presence of some red blood cells in the urine and varying degrees of

TABLE 8.—*Kidney-Function Studies in Patients with Acute Disseminated Lupus Erythematosus*

| | Patients Studied, No. | Mean | Max. | Min. |
|---|---|---|---|---|
| Phenolsulfonphthalein excretion in 2 hr. | Living 8 | 68% | 95% | 45% |
| | Died 1 | 35% | .... | .... |
| Urea clearance, cc./min. | Living 3 | 60 | 76 | 54 |
| | Died 5 | 27 | 39 | 10 |

albuminuria. In 10 of the 32 patients the blood urea nitrogen was elevated. Phenolsulfonphthalein-excretion studies for renal function were performed in nine patients, and the urea clearance was determined in eight additional instances (Table 8). One of the former and five of the latter showed considerable impairment. The renal status is an important factor in determining the prognosis of the individual patient. Evidence of progressive impairment of kidney function is, in general, an ominous sign.

False-positive serologic tests for syphilis were encountered at some time or other in more than one-third of our group.

### EFFECTS OF THERAPY

During the hospital stay of the patient a careful and complete investigation was conducted in each instance. The patients were placed on a 200 mg. (8.5 mEq.) sodium diet obtained from a special diet kitchen. The weight and blood pressure were recorded daily, and mercurial diuretics were employed in those patients in whom edema developed. In the presence of congestive heart failure a digitalis preparation was added to the regimen. Hypopotassemia and hypochloremic alkalosis were treated with the daily oral administration of 2 to 6 gm. of potassium chloride. Seventeen of the 32 patients received antibiotic therapy concomitant with the administration of the hormonal agents.

The initial daily dose of corticotropin was 100 mg., given intramuscularly in four divided doses. In the more acutely ill patients the corticotropin was admin-

istered intravenously, 20 to 40 mg. being dissolved in 500 to 1,000 cc. of 5% dextrose and given slowly over an eight-hour period. When cortisone was employed, the initial daily amount varied from 200 to 400 mg., and occasionally as much as 600 to 800 mg., given by mouth, or, more rarely, parenterally, in four divided doses. When the acute manifestations of the disease subsided, the daily amount of either drug was gradually reduced, unless there occurred a recrudescence of symptoms. The average daily maintenance dose of cortisone after the acute manifestations of the illness had been brought under control generally varied from 50 to 100 mg., while that of corticotropin varied from 25 to 75 mg. In some instances it was eventually possible to discontinue therapy entirely for variable periods of time, depending on the duration of the remission (Charts 1 and 2).

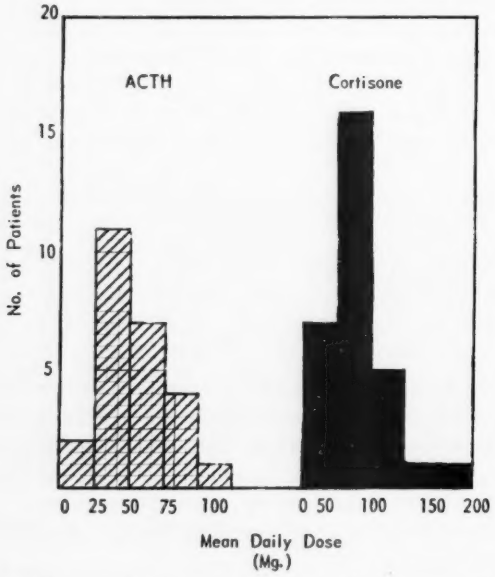


Chart 1.—Hormonal therapy of acute disseminated lupus erythematosus.

Of the group of 32 patients, 23 are living and 9 have died. Of the nine patients who died, six died of progressive renal failure, one of status epilepticus, one of a disseminated fungus infection, and one patient died during the early days of therapy, when only small amounts of the drugs were available. Of the 23 patients who are living, 8 are in a state of remission, during which they have received no hormonal treatment for 2, 3, 6, 6, 12, 17, 28, and 30 months, respectively. The remaining 15 patients require the daily oral administration of cortisone to prevent recrudescence of the illness. Of the 23 living patients, the clinical improvement was marked in 15, while improvement was moderate in character in 8 patients. Of the nine patients who died, three showed a marked temporary improvement in the clinical manifestations of the disease.

In Table 9 are listed the effects of the hormonal therapy on the acute manifestations of the disease. The fever subsided promptly in all patients. In almost two-

thirds of the patients there occurred a complete disappearance of the arthralgias, while in the remaining third the joint symptoms had lessened considerably. The rash and mucous membrane lesions disappeared almost entirely. Cardiac and pulmonary findings tended to improve with treatment, but hypertension, present before therapy was instituted, hepatomegaly, and splenomegaly persisted despite vigorous therapy. It is important to emphasize that the presence of hypertension before treatment is started usually indicates the existence of significant underlying renal disease. Psychiatric abnormalities improved in 7 of 10 patients with institution of therapy. When the psychiatric manifestations are due to the disease process, significant improvement with therapy may be reasonably expected.

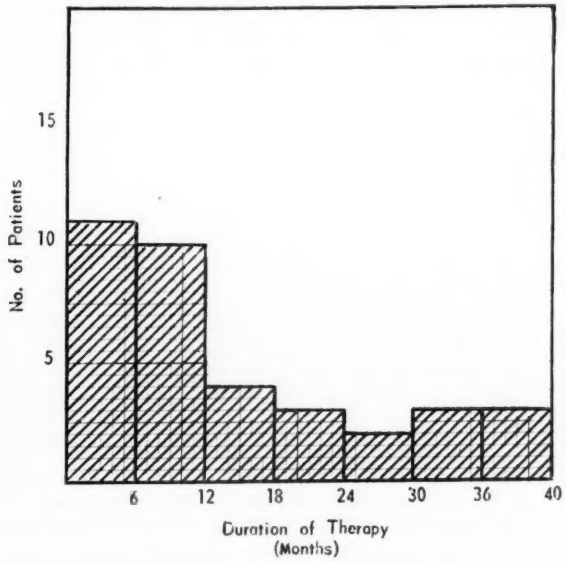


Chart 2.—Hormonal therapy of acute disseminated lupus erythematosus.

The effect of therapy on the laboratory evidence of the disease (Table 10) is by no means as satisfying as that obtained on the clinical manifestations. All patients showed the continued presence of L. E. cells in the peripheral blood. During periods of remission the cells may disappear temporarily from the bone marrow and blood, and they are certainly decreased in numbers, but a careful search will reveal their presence at some time or another. This is in contrast to the results reported by Dubois and his co-workers,[7] who found that the L. E. cells had disappeared completely within six weeks after the induction of a remission in 7 of 30 patients treated with cortisone or corticotropin. Similarly, in only a small number of patients did there occur a significant improvement in renal function, as evidenced by a decrease in the albuminuria, a reduction in the blood urea nitrogen, and a decrease in the number of red blood cells found in the urinary sediment. In some instances, the presence of an elevation of the blood urea nitrogen before institution of treatment is the result of the fever and dehydration and does not necessarily imply the exist-

ence of severe renal damage. In this group vigorous therapy will result in a decrease in the blood nitrogenous elements concomitantly with the improvement in the general clinical picture. In our experience, the persistent presence of evidence of

TABLE 9.—*Effect of Treatment with Corticotropin or Cortisone on the Clinical Manifestations of Acute Disseminated Lupus Erythematosus*

| Clinical Manifestation | Patients, No. | Patients Improved | |
|---|---|---|---|
| | | No. complete, 19 partial, 11 | % |
| Fever | 31 | 31 | 100 |
| Arthralgia | 30 | 30 | 100 |
| Weight loss | 24 | 18 | 75 |
| Lymphadenopathy | 23 | 20 | 87 |
| Rash | 23 | 20 | 87 |
| Mucous membrane lesions | 16 | 12 | 75 |
| Hepatomegaly | 14 | 0 | 0 |
| Cardiac abnormalities | 14 | 6 | 43 |
| Hypertension | 3 | 0 | 0 |
| Gallop rhythm | 3 | 2 | 67 |
| Pericardial friction rub | 3 | 2 | 67 |
| Pericardial effusion | 3 | 2 | 67 |
| Significant murmur | 2 | 0 | 0 |
| Pulmonary abnormalities | 13 | 12 | 92 |
| Pleural friction rub | 3 | 3 | 100 |
| Chest pain | 13 | 13 | 100 |
| Psychiatric abnormalities | 10 | 7 | 70 |
| Finger tip skin lesions | 8 | 4 | 50 |
| Abdominal pain | 7 | 7 | 100 |
| Edema | 7 | 5 | 71 |
| Splenomegaly | 7 | 0 | 0 |
| Alopecia | 6 | 4 | 67 |
| Fundal abnormalities | 6 | 4 | 67 |
| Neurological abnormalities | 3 | 0 | 0 |

TABLE 10.—*Effect on the Laboratory Data of Treatment with Corticotropin or Cortisone*

| Laboratory Test | Patients Before Therapy, No. | Patients Improved | |
|---|---|---|---|
| | | No. | % |
| Positive L. E. test | 32 | 0 | 0 |
| Elevated ESR | 29 | 17 | 59 |
| Hyperglobulinemia | 26 | 13 | 50 |
| WBC < 5,000/cu. mm. | 22 | 16 | 73 |
| Hemoglobin < 10 gm./100 cc. | 19 | 8 | 42 |
| Urine | | | |
| Sediment, occasional to many RBC | 17 | 5 | 29 |
| Albumin, 1+ or more | 16 | 3 | 19 |
| Abnormal chest x-ray | 12 | 7 | 58 |
| Positive serologic test for syphilis | 12 | 3 * | 60 * |
| Azotemia | 10 | 4 | 40 |
| Abnormal ECG | 8 | 3 | 38 |

* No data available in seven cases.

renal damage in the well-treated patient constitutes an ominous prognostic sign. The meager improvement in renal function following treatment has similarly been the experience of other investigators.‡ Dubois and his co-workers,[7] however, have reported a return of the renal abnormalities to normal during remissions.

‡ References 8 and 9.

An elevation of the sedimentation rate was present in 29 of the 32 patients in our series. Following the induction of a remission with therapy, the sedimentation rate became considerably reduced in 17 members of this group. It is of some interest to note that hyperglobulinemia, present in approximately an equal number of patients, was similarly lowered in half the group after treatment. Recrudescence of the disease was often heralded by an increase in the sedimentation rate before more overt manifestations became evident. More than half the patients of the entire group had a considerable degree of anemia, with hemoglobin levels less than 10 gm. per 100 cc. Improvement in the anemia occurred slowly, over a prolonged period of time, and in only approximately 40% of the patients did the hemoglobin levels eventually attain normal peaks. The two patients with a clinical hemolytic syndrome and positive Coombs test responded well to treatment. In both instances the evidence of hemolysis disappeared and both the red blood cell counts and the hemoglobin levels increased appreciably. The leucopenia, present in 22 of the 32 patients,

TABLE 11.—*Complications of Treatment with Corticotropin or Cortisone*

| Manifestation | Living Patients | | Patients Who Died | | Total | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Rounding of face | 17 | 74 | 7 | 77 | 24 | 75 |
| Psychiatric abnormalities | 13 | 57 | 7 | 77 | 20 | 63 |
| Hypertension | 9 | 39 | 9 | 100 | 18 | 56 |
| Edema | 8 | 35 | 8 | 88 | 16 | 50 |
| Infections | 10 | 44 | 5 | 55 | 15 | 47 |
| Acne | 10 | 44 | 3 | 33 | 13 | 40 |
| Alopecia | 7 | 30 | 3 | 33 | 10 | 31 |
| Hirsutism | 6 | 26 | 3 | 33 | 9 | 28 |
| Convulsions | 2 | 9 | 6 | 67 | 8 | 25 |
| Congestive heart failure | 1 | 4 | 6 | 67 | 7 | 22 |
| Metabolic alkalosis | 3 | 13 | 3 | 33 | 6 | 19 |
| Abdominal striae | 2 | 9 | 3 | 33 | 5 | 16 |
| Diabetes | 1 | 4 | 1 | 11 | 2 | 6 |
| Osteoporosis | 0 | 0 | 1 | 11 | 1 | 3 |
| Peptic ulcer | 1 | 4 | 0 | 0 | 1 | 3 |

responded well to treatment, and in three-fourths of the patients the white blood cells attained normal levels during remissions.

Convulsive episodes occurred in eight patients at one time or another during the course of the illness. In patients under treatment it is difficult to determine whether such episodes are the result of the illness or are drug-induced. The former calls for more vigorous therapy, while in the latter instance treatment must be discontinued temporarily. Convulsions may occur as part of the clinical manifestations of severe acute disseminated lupus.§ The incidence of such seizures, however, appears to be greater in those patients receiving treatment with cortisone or corticotropin.

### COMPLICATIONS OF TREATMENT WITH CORTISONE OR CORTICOTROPIN

Since acute disseminated lupus erythematosus is a disease which requires treatment with large amounts of cortisone or corticotropin over a prolonged period of time, it is not astonishing that one or more side-effects attributable to the hormones occur in a considerable number of patients (Table 11). In addition, there are

§ References 10 and 11.

certain side-effects which occur with a greater degree of frequency in this condition than under other circumstances. Hypertension as a result of treatment was found in more than half the patients, despite the fact that the patients were maintained on a rigid low-sodium diet. Of the nine patients who died, all had hypertension, while only slightly more than one-third of those who have survived developed this complication. Of this latter group, in all instances but one the blood pressure returned to normal levels after adequate reduction in dosage of the hormonal agents. The patient whose blood pressure failed to return to normal levels had had a previous sympathectomy for severe hypertension. It is our impression that hypertension following treatment is considerably more prone to occur in the presence of renal or vascular disease. Hence it is much more often encountered during therapy in patients with acute disseminated lupus erythematosus or periarteritis nodosa than in those illnesses in which underlying renal or vascular disease is absent. Varying degrees of edema were encountered in half the group and actual congestive heart failure in almost 22%. Both the edema and the heart failure may be rendered minimal by a rigid adherence to a salt-free diet with limited fluid intake. When the dosage of the drug could not be safely reduced and edema persisted, mecurial diuretics were cautiously administered. In addition, some form of digitalis preparation was employed in the presence of congestive failure.

One or more of the usual manifestations of Cushing's syndrome, such as rounding of the facies, acne, hirsutism, bright red abdominal striae, and alkalosis, occurred in almost all the members of the treated group. Hypochloremic alkalosis, which was encountered in almost 20% of the patients, is a hazardous complication, since it usually bespeaks the existence of a significant reduction in the potassium stores. To correct this defect, when it was present, potassium chloride was administered either orally or parenterally in doses of 2 to 6 gm. daily. More recently, the routine daily use of potassium chloride has been incorporated in the treatment schedule to prevent the development of this side-effect.

Some form of mental aberration appeared during the course of treatment in almost two-thirds of the patients. Such mental changes may be manifested by euphoria, depression, or actual paranoid trends. With reduction in dosage of the hormone these manifestations tended to disappear. In some instances complete discontinuance of therapy was necessary and, rarely, shock treatment had to be resorted to to control the severe depression. In cases in which the psychotic patterns subsided when treatment was discontinued, subsequent resumption of therapy did not always result in a return of the mental symptoms.

Hyperglycemia and glycosuria occurred in two patients, osteoporosis in one patient, and a peptic ulcer in one patient. With a reduction in the dosage schedule, the hyperglycemia and glycosuria disappeared. The osteoporosis occurred in a woman in the postmenopausal age. Roentgenographic study of the spine revealed marked osteoporosis, with a compression fracture of the first lumbar vertebra and considerable narrowing of the 12th thoracic vertebra. It was our impression that this patient had some postmenopausal osteoporosis that had been intensified by the prolonged use of cortisone. The administration of methyltestosterone for a long period of time resulted in a decrease in the back pain, but this improvement was not associated with any x-ray evidence of recalcification of the vertebral column.

Most of the side-effects resulting from therapy are reversible when progress in the clinical condition of the patient permits a reduction in the dosage or discontinuance of hormone therapy. Complications such as hypertension, edema, congestive heart failure, psychiatric abnormalities, convulsions, and alkalosis, however, occur with a considerably greater degree of frequency in those patients who eventually die of the disease than in those who survive. This is probably a reflection of the greater severity of the illness in the former group and, therefore, of the necessity for larger amounts of the hormonal agents administered over a more prolonged period of time.

SUMMARY

Thirty-two patients with acute disseminated lupus erythematosus were treated with cortisone or corticotropin. This series includes 26 females and 6 males. Their ages vary from 11 to 60 years, but the greatest incidence of the disease occurred during the second, third, and fourth decades.

This study extends over a period of 40 months. Our most recent patient has been under observation and treatment for 1 month, our oldest for 40 months.

Of the 32 patients, 23 are living and reasonably well and 9 have died.

Of the 23 who are living, 8 are in a state of remission without treatment, thus far lasting from 2 to 30 months. The remaining 15 patients require continued hormonal therapy on a maintenance basis.

Of the nine patients who died, six succumbed to progressive renal failure, one to status epilepticus, one to a disseminated fungus infection, and one to inadequate therapy.

The clinical manifestations of the disease, which are very varied, are described. Fever and arthralgias occurred in almost all patients. Significant weight loss, the characteristic rash, and a diffuse lymphadenopathy were encountered in three-fourths of the patients. Some form of cardiac or pulmonary abnormality and typical mucous membrane lesions were seen in half the group. Hepatomegaly, splenomegaly, or both were not infrequently found.

Almost all the patients had either a normal white blood cell count or a leucopenia, and most showed varying degrees of anemia. A positive Coombs test was demonstrated in four patients, and two of these had a clinical hemolytic syndrome. A significant thrombocytopenia was found in two patients.

Typical L. E. cells were demonstrated in the peripheral blood in all members of the series, and the sedimentation rate was found to be elevated in 90% of the group. Slightly more than half the patients had evidence of renal disease, and a third showed a definite elevation of the blood urea nitrogen. More than a third of the group had false-positive serologic tests for syphilis.

The effects of treatment on the clinical manifestations are described. Hypertension present before institution of therapy, renal abnormalities, hepatomegaly, and splenomegaly responded either poorly or not at all to the hormone therapy. The lupus cells persisted during hormone-induced remission, although they were much reduced in number and more difficult to find. The remaining clinical and laboratory manifestations improved to varying degrees.

The complications resulting from treatment with cortisone or corticotropin are discussed. Almost all patients developed some evidence of hypercorticalism. Hypertension, edema, congestive heart failure, psychiatric abnormalities, convulsions,

and alkalosis occurred with a greater degree of frequency in the patients who died than in those who are living. The side-effects of hormonal therapy are generally reversible when the dosage is reduced or treatment is entirely discontinued.

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# LISTERIA MONOCYTOGENES MENINGITIS

## Summation of Literature and Report of Two New Cases

SYDNEY M. FINEGOLD, M.D.
LOS ANGELES
JOHN G. BRADLEY, M.D.
MALCOLM K. CAMPBELL, M.D.
AND
ALBERT J. GREENBERG, M.D.
MINNEAPOLIS

ALTHOUGH infections due to Listeria monocytogenes are common among animals throughout the world, the organism has not often been associated with human infections. Listeria organisms have been isolated from man in only two types of conditions—infectious mononucleosis and meningitis. The relationship of this organism to infectious mononucleosis is dubious, the literature on the subject having been reviewed and discussed recently by Girard and Murray (1951).

The first authenticated case of Listeria meningitis was reported by Burn in 1935. However, Dumont and Cotoni reported, in 1921, a case of meningitis stated to be due to a diphtheroid, which was subsequently identified as a Listeria, and Atkinson reported five cases of meningitis due to diphtheroids as early as 1917 (before L. monocytogenes was recognized as a species). There are five other cases of meningitis caused by diphtheroids reported in the literature; in two of these the organisms were definitely identified as Listeria subsequent to the original reports. It appears that the other eight diphtheroids may have actually been Listeria in view of the marked similarity of the organisms and the known capacity of Listeria to cause meningitis. Table 1 summarizes the case reports in the literature. Including the cases due to "diphtheroids," there have been 37 reported cases of Listeria meningitis up to the time of the present report. The reporting of 11 cases in the last five years suggests that this infection is more prevalent than was previously recognized.

The present cases are the first to be reported from Minnesota, and these patients are the oldest known to have survived the disease.

### REPORT OF CASES

CASE 1.—R. O., a 68-year-old white married traveling rug salesman, was admitted to the Minneapolis General Hospital on April 15, 1952. He had been well until April 6, when he developed a "chest cold." He was able to continue working until April 11, when he developed fever, severe postorbital and suboccipital headache, anorexia, and vomiting. On April 12 the patient noted stiffness and aching of the neck. On April 13 his physician was called, because of persistence of these symptoms, and he prescribed chlortetracycline (Aureomycin). One dose

Dr. Finegold is with the Department of Internal Medicine, Wadsworth Veterans Hospital.
From the Departments of Internal Medicine, Minneapolis General Hospital and the University of Minnesota Hospitals and Medical School, Minneapolis.

TABLE 1.—*Cases of Meningitis Due to Listeria or Diphtheroids*

| Authors | Location | Age | Blood Culture | Spinal Fluid Culture | Specific Treatment | Outcome |
|---|---|---|---|---|---|---|
| Atkinson, 1917 | Australia | 2 yr. | Not done | Diphtheroid | None | Death |
| Atkinson, 1917 | Australia | 4 yr. | Not done | Diphtheroid | None | Death |
| Atkinson, 1917 | Australia | 3¾ yr. | Not done | Diphtheroid | None | Death |
| Atkinson, 1917 | Australia | 9 yr. | Not done | Diphtheroid | None | Death |
| Atkinson, 1917 | Australia | 2 yr. | Not done | Diphtheroid | None | Recovery |
| Dick, 1920 | Illinois | 49 yr. | Diphtheroid | Diphtheroid | None | Death |
| Dumont & Cotoni, 1921 | France | 24 yr. | Negative | Diphtheroid* | None | Death |
| Kessel & Romanoff, 1930 | New York | 39 yr. | Diphtheroid | Diphtheroid | None | Recovery |
| Schultz & others, 1934 | California | "Adult" | Not done | Diphtheroid* | None | Recovery |
| Tesdal, 1934 | Norway | 31 yr. | Negative | Diphtheroid | None | Death |
| Gibson, 1935 | Scotland | 37 yr. | Not done | Diphtheroid* | None | Death |
| Burn, 1935 | Connecticut | 26 yr. | Not done | Listeria isolated from brain | None | Death |
| Burn, 1936 | Connecticut | 1 day | Listeria | ..... | None | Death |
| Burn, 1936 | Connecticut | Premature infant | Listeria | ..... | None | Death |
| Burn, 1936 | Connecticut | 8 days | Listeria | Listeria | None | Death |
| Burn, 1936 | Connecticut | 53 yr. | Listeria and Type 3 Pneumococcus isolated from brain | | None | Death |
| Carey, 1936 | Massachusetts | 3¾ yr. | Not done | Listeria | None | Recovery |
| Poston & others, 1937 | North Carolina | 3 yr. | Not done | Listeria isolated from brain | None | Death |
| Porzecanski & de Baygorria, 1938 | Uruguay | 19 yr. | Not done | Listeria | Azosulfamide | Recovery |
| Wright & MacGregor, 1939 | Scotland | 1½ yr. | Not done | Listeria | None | Death |
| Porter & Hale, 1939 | Iowa | "Child" | Listeria isolated, source? | | Sulfanilamide | Recovery |
| Savino, 1940 | Argentina | 67 yr. | Negative | Listeria | Sulfapyridine | Recovery |
| Kapsenberg, 1941 | Netherlands | 3 yr. | Listeria | Listeria | None | Death |
| Kapsenberg, 1941 | Netherlands | 14 days | Not done | Listeria (ventricular fluid) | None | Death |
| Kapsenberg, 1941 | Netherlands | "Child" | Not done | Listeria | None | Residual hydrocephalus; short follow-up |
| Kapsenberg, 1941 | Netherlands | 39 yr. | Not done | Listeria | Sulfapyridine | Recovery |
| Handelman & others, 1946 | Kentucky | 6 wk. | Negative | Listeria | Sulfadiazine, penicillin | Recovery |
| Martin & others, 1947 | France | 57 yr. | Not done | Listeria | Sulfonamide, penicillin | Death |

| | | | | | | |
|---|---|---|---|---|---|---|
| van Driest, 1948 | Netherlands | 10 days | Listeria isolated, source? | | Sulfadiazine, penicillin | Recovery; possible residual hydrocephalus |
| Slooff, 1948 | Netherlands | 10 days | ..... | * Listeria | Sulfadiazine, penicillin | Recovery |
| Beute & others, 1948 | Netherlands | 3 wk. | Not done | Listeria | Sulfathiazole, sulfadiazine | Recovery |
| Stanley, 1948 | Australia | 79 yr. | Not done | Listeria | None | Death |
| Berry, 1950 | Maryland? | 32 yr. | Negative | Listeria | Sulfadiazine, penicillin, streptomycin | Recovery |
| Line & Cherry, 1952 | Tennessee | 11 days | Not done | Listeria | Sulfadiazine, penicillin, streptomycin | Death |
| Line & Cherry, 1952 | Tennessee | 6 days | Not done | Listeria | Sulfadiazine, penicillin, chloramphenicol, dihydrostreptomycin, chlortetracycline | Residual hydrocephalus; died after surgery at 9 mo. age |
| Bennett & others, 1952 | Georgia | 15 yr. | Listeria | Listeria | Sulfadiazine, penicillin, chloramphenicol, oxytetracycline | Recovery |
| Line & Appleton, 1952 | Tennessee | Premature infant, 5 days | Listeria | Listeria | Sulfadiazine, penicillin, chloramphenicol, dihydrostreptomycin, chlortetracycline, oxytetracycline | Recovery |
| Finegold & others (present report) | Minnesota | 68 yr. | Negative | Listeria | Sulfadiazine, sulfisoxazole, penicillin, chlortetracycline, streptomycin | Recovery |
| Finegold & others (present report) | Minnesota | 68 yr. | Negative | Listeria | Sulfadiazine, penicillin, streptomycin, chlortetracycline | Recovery; residual ptosis left lid |

* Subsequently identified as Listeria.

of 500 mg. was given to the patient the evening of April 13, but he vomited this medication shortly thereafter. After a restless night, the patient appeared generally worse on the morning of April 14 and was hospitalized at another hospital in Minneapolis on this date. Past history, family history, and review of systems were essentially negative. There was no exposure to animals and no other known contact with a possible source of infection. Pertinent physical findings were moderate nuchal rigidity, generalized decrease in deep tendon reflexes, and a few medium moist rales at the base of the left lung. The sensorium was clear.

Lumbar puncture done at 6:00 p. m. April 14 revealed a turbid spinal fluid under an initial pressure of 290 mm.; the fluid contained 400 cells, with 76% polymorphonuclear and 24% mononuclear cells; protein was 350 mg. and sugar, 87 mg. per 100 cc. The patient had received dextrose intravenously. A stained film of the spinal fluid showed no organisms, but the culture contained a Gram-positive bacillus. A blood culture was sterile. The white blood cell count was 17,450, with 77% polymorphonuclear cells, 7 lymphocytes, and 16 monocytes. An x-ray of the chest revealed an infiltrative process at the base of the left lung.

Initial treatment consisted of 400,000 units of penicillin intramuscularly at 12:30 p. m. After the lumbar puncture 300,000 units were administered every three hours for two doses and subsequently, 400,000 units every two hours. The patient also received 1.0 gm. of sodium sulfadiazine intravenously at 11:00 p. m. and 1.5 gm. of sulfisoxazole (Gantrisin) orally at 4:00 a. m.

The patient was transferred to the Minneapolis General Hospital the morning of April 15. Physical examination at that time revealed an acutely ill elderly man who appeared toxic, confused, and very restless. His temperature was 102 F., pulse rate 110, respiration rate 18 per minute, and blood pressure 134/78. Marked nuchal rigidity was present; there were a positive Brudzinski's sign and a questionably positive Kernig's sign. The pupils were equal but reacted poorly to light and in accommodation. Fundoscopic examination revealed only slight arteriolar narrowing. The right frontal sinus did not transilluminate. There was minimal subjective mastoid tenderness bilaterally. The heart was slightly enlarged to the left, the left border of cardiac dullness being 13 cm. from the midsternal line. Neurological examination revealed, in addition to the poorly reacting pupils, depressed but equal deep tendon reflexes, a weak left cremasteric reflex, and absent abdominal reflexes. Results of the remainder of the physical examination were normal.

The blood Wasserman test was negative. The hemoglobin was 15.8 gm. and the white blood cell count was 15,000 on April 15. Urinalysis on April 15 showed 2+ albumin and 3 to 4 red blood cells per high-power field. The patient had a persistent low-grade eosinophilia (eosinophiles 2 to 7%) from April 21 until his discharge from the hospital. On April 15 the blood urea nitrogen was 23 mg. per 100 cc., $CO_2$-combining power 18.3 mEq. per liter, and chlorides 99 mEq. per liter. The blood urea nitrogen remained at approximately the same level on several repeat examinations. The $CO_2$-combining power was 25 mEq. per liter on April 16 and subsequently remained normal, as did the chlorides. The serum albumin was 4.01 gm. and serum globulin 2.23 gm. per 100 cc. The total serum bilirubin was 0.52 mg. per 100 cc., and the thymol turbidity was 1 unit. The cephalin-cholesterol-flocculation test was negative. The 24-hour urine urobilinogen was 2 mg. There was 30% retention of sulfobromophthalein (Bromsulfalein) dye at 45 minutes; unfortunately, this was not repeated. Since the patient was a rather large man, this sulfobromophthalein test may not have been very abnormal. The heterophile titer was 1:7. Nose and throat cultures revealed only coagulase-positive and coagulase-negative staphylococci. Blood cultures on entry showed no growth. Urine smear and culture were negative for pathogens. The spinal fluid on entry was under a pressure of 290 mm.; the fluid contained 2,000 cells, with 65% mononuclear cells; protein was 356 mg., sugar 48 mg., and chlorides 658 mg. per 100 cc., and a Gram-positive bacillus was obtained on culture. The following day the spinal fluid pressure was 278 mm; there were 1,200 cells, with 62% mononuclear cells; protein was 292 mg., sugar 51 mg., and chlorides 638 mg. per 100 cc. Culture was again positive. On April 22 the spinal fluid pressure was 96 mm.; there were 371 cells, all mononuclear cells; protein was 152 mg., sugar 75 mg., and chlorides 718 mg. per 100 cc. On April 28 the spinal fluid pressure was 152 mm.; there were 32 cells, with 83% polymorphonuclear cells; protein was 82 mg. and sugar 81 mg. per 100 cc. Culture of the last two spinal fluids yielded no growth. The sugar values are thought to be unreliable because of administration of intra-

venous dextrose. Several electrocardiograms revealed tachycardia, left ventricular hypertrophy and strain pattern, and premature ventricular contractions. Chest x-rays April 15, April 18, and April 22 revealed only slight left ventricular prominence, with clear lung fields. X-rays of the mastoids and sinuses revealed no abnormalities except for a poorly developed right frontal sinus.

The patient was admitted to the station at 11:00 a. m. and was given a sedative and restrained. Treatment was begun with chlortetracycline, 500 mg. intravenously every eight hours. The patient became worse during the first few hours. At 4:15 p. m. his temperature was 105.6 F. rectally and he did not respond to painful stimuli. He then began to improve slowly. By 6:30 p. m. he responded slightly. At 8:00 p. m. his temperature was 103.2 F. (rectal) and he muttered in response to questions. Starting at 9:00 p. m. the patient was given 1.0 gm. of dihydrostreptomycin intramuscularly every eight hours in addition to the intravenously administered chlortetracycline. Other treatment was symptomatic and consisted mainly of intravenous fluids during the first four days.

The patient's blood pressure remained stable throughout his hospital stay. His temperature fell gradually to normal by April 21 and remained normal. His course was one of gradual improvement. He remained confused, occasionally disoriented, and restless on April 16 and then became quite clear, although drowsiness persisted another two days. The patient was able to take 2,500 cc. of fluids orally April 16 and ate a soft diet on April 17. He required no sedation after April 16. By April 18 the patient was quite alert and cheerful and offered no complaints; weak abdominal reflexes were present on this date. In the evening on April 18 fine moist rales appeared at both lung bases and the circulation time was 18 seconds. The patient was digitalized, and the rales cleared. On April 23 the patient was arbitrarily taken off dihydrostreptomycin and started on penicillin because of persistent leucocytosis, although his clinical condition was excellent. On April 24 a fine morbilliform rash appeared on the trunk; this disappeared in a short time with treatment with diphenhydramine (Benadryl). A leucocyte count of 33,000 on April 24 was associated with a urinary infection, which resolved spontaneously. There was a prolonged low-grade leucocytosis and mild eosinophilia, thought possibly to represent a drug reaction.

The patient's convalescence was otherwise uneventful, and he was discharged on May 9, five days after all therapy was stopped. Neurological examination at the time of discharge showed no abnormalities. The patient has remained well, without evidence of relapse or residual. He returned to work early in July.

CASE 2.—J. K., a 68-year-old white carpenter, was admitted to the Minneapolis General Hospital, on Oct. 25, in a semicomatose state. The only history obtained on admission was from friends, who found him comatose in his boarding house room at 1:00 p. m. that day. He could not be aroused and was brought to the hospital by ambulance, arriving at 6:00 p. m. He had apparently been in good general health up until the previous day, when he complained of feeling chilly and fatigued. After the evening meal he retired; he was found comatose the following afternoon. No shaking chills or convulsions were observed by friends. There was no known contact with animals. Past history revealed that the patient had had "black measles" followed by pneumonia at the age of 35. His wife gave a history of previous hypertension, but the patient subsequently denied this. The patient admitted to drinking about a pint of whiskey a week for the past 20 years. The family history was noncontributory. Review of systems was negative except for frequency and urgency of urination and nocturia during the past year.

Physical examination revealed an obese plethoric slightly cyanotic semicomatose white man. His temperature was 105 F. rectally, pulse rate 86, respiration rate 30 per minute, and blood pressure 160/95. He reacted only to painful stimuli. Positive physical findings were as follows: The left pupil was widely dilated, and a definite ptosis of the left lid was noted. The fundi showed moderate arteriolar narrowing and constriction but no papilledema. The breath was extremely foul, with the tongue dry and furry. The teeth were in poor condition. The neck was rigid and could not be flexed more than 10 degrees. There were scattered crepitant rales at the base of the left lung. A Grade II systolic apical murmur was heard; the heart was not enlarged. The liver was precussed 4 cm. below the costal margin, but no definite edge was felt. The testes were atrophic. Rectal examination revealed a relaxed sphincter and Grade III

smooth symmetrical enlargement of the prostate. In addition to the left third nerve paralysis, neurological examination revealed a left seventh nerve paralysis; biceps, triceps, patellar, and Achilles responses were equal and hypoactive. Superficial reflexes were equal and normal.

The blood Wassermann test was negative. The hemoglobin was 15.4 gm. on entry; white blood cell count was 16,800, with 87% polymorphonuclear cells, and the sedimentation rate was 72 mm. in one hour. Urinalysis on admission showed a specific gravity of 1.032, with 2+ albumin, 3+ sugar (after dextrose intravenously), many red blood cells, and 10 to 15 WBC per high-power field. Spinal fluid on admission showed an initial pressure of 280 mm.; the fluid was milky and contained 2,550 white cells, with 94% polymorphonuclear and 6% mononuclear cells. Spinal fluid protein was 272 mg. and sugar 44 mg. per 100 cc. (patient had received dextrose intravenously); no organisms were seen in a direct smear, but the culture grew out a Gram-positive bacillus similar in appearance to that from the first case. Two blood cultures drawn the day of admission were negative for pathogens. Nose and throat cultures grew out only coagulase-negative Staphylococcus albus. Chest x-ray showed a calcified area in the upper lobe of the right lung, with a rather large mass of calcified parabronchial nodes on the right side. The blood urea nitrogen was 12 mg. per 100 cc., the $CO_2$-combining power 25.4 mEq. per liter, chlorides 106 mEq. per liter, and blood sugar 179 mg. per 100 cc. (patient had been given dextrose). Subsequent blood urea nitrogen, $CO_2$, chloride, and blood sugar determinations were within normal limits. The total serum bilirubin was 1.1 mg. per 100 cc., thymol turbidity 7.7 units, serum albumin 3.88 gm. per 100 cc., and serum globulin 3.92 gm. per 100 cc., and the prothrombin time was 16.6 seconds for the patient, with a control of 13.5 seconds. There was 2% retention of sulfobromophthalein after 45 minutes. The heterophile titer was 0. The hemoglobin gradually fell to 12.0 gm. by Dec. 5. The white blood cell count was 16,600 with 83% polymorphonuclear cells on Oct. 28. On Nov. 14 the white blood cell count was 21,300, with 77% polymorphonuclear cells, and on Dec. 5 it was 11,500, with 73% polymorphonuclear cells. The eosinophiles varied between 3 and 9%. Urinalysis on Oct. 28 showed 1+ albumin, with 50 RBC and 14 WBC per high-power field. Subsequent urinalysis on two occasions revealed no albumin and small numbers of both red blood cells and white blood cells. A repeat spinal tap, on Oct. 27, showed an initial pressure of 227 mm., with 528 cells, of which 68% were polymorphonuclear cells, and protein 112 mg., sugar 42 mg., and chlorides 668 mg. per 100 cc. Spinal tap on Nov. 1 showed a pressure of 210 mm., with 194 white cells, 68% of which were mononuclear cells, protein 100 mg., sugar 54 mg. On Nov 14 the spinal fluid was under a pressure of 150 mm. and contained 7 WBC, all of which were mononuclear cells; protein was 383 mg., sugar 45 mg., and chlorides 736 mg. per 100 cc. A final tap, Dec. 9, yielded fluid under a pressure of 150 mm.; this fluid contained 17 white cells, 90% of which were mononuclear cells, and had protein 54 mg., sugar 54 mg., and chlorides 760 mg. per 100 cc. Smears and cultures of these last four spinal fluid specimens were all negative for pathogens. An electrocardiogram on Oct. 26 showed a sinus rhythm, with frequent premature ventricular contractions, left axis deviation, and depressed ST segments in Leads I, II, $aV_L$, $V_4$, and $V_6$; the T waves were inverted in Leads I, $aV_L$, and $V_6$. A repeat tracing, Nov. 28, showed less ST-segment depression generally and reversion of the T waves to positive. On Oct. 31 an x-ray of the mastoids was normal and a repeat chest x-ray showed no change. X-rays of the skull on Nov. 19 showed no abnormalities. On Nov. 28 x-rays of the sinuses revealed slight cloudiness of the maxillary sinuses with thickened mucous membranes bilaterally, consistent with chronic maxillary sinusitis.

On admission the patient was given intravenous fluids. An oral airway was inserted, and suction was frequently necessary during the first five days. An indwelling catheter was inserted into the urinary bladder, and oxygen was administered by nasal catheter. Antibiotic treatment was given as follows: Aqueous penicillin G 1,000,000 units was given intravenously every four hours for 9 days, beginning Oct. 25; aqueous penicillin G 1,000,000 units was given intramuscularly every three hours for 31 days, beginning Oct. 25. Sulfadiazine and sodium bicarbonate were started on Oct. 25 but were discontinued after one dose of 5 gm. of sulfadiazine, because of low urinary output. In addition, the patient received streptomycin 0.5 gm. intramuscularly every six hours for 11 days, beginning Oct. 26, and chlortetracycline 500 mg. intravenously every eight hours for four days, beginning Oct. 27 (the latter had to be discontinued because of widespread thrombophlebitis). The temperature gradually fell to normal by the 11th hospital day and remained normal subsequently. The blood pressure was stable throughout the course of the

illness. The patient had to be maintained for one week on parenteral fluids. Coarse tremors of all extremities were noted for the first week. The urinary output was poor during the first 48 hours and then a normal output occurred. On Oct. 27 the patient recognized his relatives but could not speak. On Nov. 1 he began to talk in a garbled fashion. He was still incontinent of feces and the left third and seventh nerve paralyses persisted; at times he would lapse into a semicomatose state. By Nov. 5 he started taking fluids by mouth well; his speech improved; he became more alert; he was able to sit up in bed, and he was afebrile for the first time. By Nov. 8 he was eating a regular diet well, was sitting up often, and was well oriented and the third and seventh nerve paralyses were improving. The indwelling catheter was removed but had to be reinserted because of urinary retention. On Nov. 19 the patient was up in a chair for the first time. By Dec. 5 he was able to walk around and the seventh nerve paralysis had disappeared. The only residual of the third nerve paralysis is ptosis of the left lid. The patient is presently alert, cheerful, and cooperative. The prolonged leucocytosis and eosinophilia were thought to possibly represent a drug reaction. The abnormal liver-function tests may have been related to alcoholism.

## SPECIAL STUDIES

*Bacteriologic Studies.**—The organisms isolated from all four spinal fluid cultures from the two patients were similar. They were Gram-positive pleomorphic rods. At times the morphology was quite regular, with rounded ends and palisading, the organism closely resembling a diphtheroid. Other subcultures revealed moderate pleomorphism with coccoid and filamentous forms and rods with straight, rather than tapered, ends. The organisms stained quite homogeneously with methylene blue. In the case of the Listeria recovered from Patient R. O., motility (end-over-end) was noted only after the organism was passed through a mouse; motility was readily demonstrated in a broth culture of the organism from Patient J. K.

The cultures grew readily on blood agar, Trypticase-Soy broth, and dextrose broth. Fair growth was obtained on nutrient agar. On blood agar, small (2 mm. diameter) flat delicate gray-white colonies appeared in 24 hours; these colonies were much like those produced by diphtheroids or streptococci. A small zone of beta hemolysis about the colonies was apparent after 24 to 48 hours.

Growth on Loeffler's medium and on gelatin was not accompanied by liquefaction. Urea was not hydrolyzed and indole was not formed. The methyl red test was positive, and the Voges-Proskauer test was negative. Fermentation reactions of the organism from Patient R. O. were as follows: Acid was produced from dextrose, maltose, xylose, salicin, rhamnose, and galactose. Acid was produced slowly from mannitol, lactose, and arabinose, and very slowly from sucrose. Dulcitol, inositol, and inulin were not fermented.

Intraperitoneal injection of a white mouse with 0.4 cc. of an 18-hour broth culture of the organism from Patient R. O. killed the animal overnight. The only pathologic lesions noted grossly were hemorrhagic areas in both lungs. The organism was recovered from the lungs, liver, and spleen.

One drop of an 18-hour broth culture of Listeria from Patient R. O. dropped into the conjunctival sac of a rabbit resulted in a conjunctivitis of moderate severity

* Dr. Newell R. Ziegler, Associate Professor of Bacteriology, University of Minnesota, first suggested that the organism isolated from patient R. O. might be a Listeria, and Mrs. Lillian Helfman, Department of Bacteriology, Minneapolis General Hospital, gave assistance in identifying the first culture and identified the culture from the second patient. Dr. Henry Bauer, of the Minnesota State Board of Health, confirmed the identification of the culture from the first case.

which subsided spontaneously in 10 days. No keratitis resulted. Gently swabbing the upper tarsal conjunctiva of a rabbit with a swab dipped in the same 18-hour broth culture of this organism gave rise to a much more severe infection. A mild conjunctivitis was present after 24 hours; at 48 hours the conjunctivitis had become severe, with considerable purulent discharge. At 48 hours an early keratitis was noted, and at 96 hours the cornea was diffusely hazy. Subsequently, four 1 to 2 mm. ulcerations were noted in the cornea (at 6 days) and small vessels grew in toward the pupil from the periphery (10 days). The organism was recovered on culturing the eye six days after inoculation. At 22 days the conjunctivitis had subsided entirely and only a little corneal injection and haziness remained. A few small corneal scars remained permanently. A similar reaction was observed in another rabbit's eye after the lid was swabbed with an 18-hour broth culture of Listeria from Patient J. K. The eye which had been infected with Listeria from Patient R. O. was subsequently challenged (one month following the original inoculation) with a known Listeria (Listeria 813)‡ by swabbing the tarsal conjunctiva with an 18-hour broth culture; no infection resulted, thus demonstrating a local immunity. The same culture of

TABLE 2.—*Sensitivity of Six Strains of Listeria to Seven Antibiotics (Tube-Dilution Method)**

| | Listeria Strain | | | | | |
|---|---|---|---|---|---|---|
| | R. O. | J. K. | Baptist | CD | RE | 813 |
| Penicillin | 0.75 | 0.38 | 0.75 | 0.75 | 0.75 | 0.75 |
| Streptomycin | 12.5 | 3.1 | 6.3 | 3.1 | 6.3 | 6.3 |
| Chlortetracycline | 0.75 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Oxytetracycline | 0.75 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Chloramphenicol | 6.3 | 6.3 | 12.5 | 12.5 | 12.5 | 12.5 |
| Bacitracin | 1.5 | 1.5 | 1.5 | 1.5 | 3.1 | 3.1 |
| Neomycin | 3.1 | 0.75 | 1.5 | 1.5 | 1.5 | 1.5 |

* The figures given are in terms of units per cubic centimeter for penicillin and bacitracin and in γ per cubic centimeter for the other antibiotics.

Listeria 813, at the same time, was instilled in a similar fashion into another rabbit's eye, and the characteristic keratoconjunctivitis developed. The culture of Listeria from Patient R. O. also produced a keratoconjunctivitis in a guinea pig's eye after inoculation by swabbing.

Sensitivity studies with antibiotics were done on Listeria strains from Patients R. O. and J. K. and on four others (strain 813 § and strains Baptist, CD, and RE ‖). The last four strains were also isolated from cases of human meningitis. The tube-dilution technique was used in these studies (Waisbren and co-workers, 1951). The organisms were grown in Trypticase-Soy broth, and the inoculum used was a 1 : 100 dilution of an 18-hour culture in Trypticase-Soy broth; the tests were incubated for 18 hours at 37 C. Results of these tests are given in Table 2. The antibiotic sensitivity was remarkably consistent from strain to strain. All organisms were fairly sensitive to penicillin, streptomycin, chlortetracycline, oxytetracycline (Terramycin), bacitracin, and neomycin and somewhat less sensitive to chloramphenicol.

‡ Strain 813 was supplied by Dr. Martha K. Ward, Communicable Disease Center, United States Public Health Service, Chamblee, Ga.

§ Strain 813 was supplied by Dr. Martha K. Ward, Communicable Disease Center, United States Public Health Service, Chamblee, Ga.

‖ Strains Baptist, CD, and RE were supplied by Dr. William B. Cherry, Communicable Disease Center, United States Public Health Service, Chamblee, Ga.

*Immunologic Studies.*—Acute and convalescent sera were obtained from Patient R. O. on the 15th and 52nd day after onset of the illness, respectively, and were studied for the presence of agglutinins against the patient's own Listeria and L. CD and L. 813. The organisms were grown in Trypticase-Soy broth, and the antigens were prepared by formalinizing the cultures according to the suggestions of Line and Cherry, 1952. Serial twofold dilutions of serum in final concentrations ranging from 1:20 to 1:1,280 were used. Five-tenths cubic centimeter amounts of both antigen and serum dilution were used. No agglutination was noted in any of the tests after four hours incubation in a 37 C. water bath. Final readings made after overnight refrigeration revealed partial agglutination of the patient's own Listeria in a titer of 1:40 with the acute serum and partial agglutination in a titer of 1:80 with the convalescent serum; no agglutination of the other two organisms was obtained. The agglutination noted was of the granular type.

The evidence of local immunity produced in a rabbit's eye after infection with Listeria from Patient R. O. has already been cited.

## COMMENT

L. monocytogenes was first submitted as a new species in 1924.

The organism cannot be completely identified by its morphology, colonial appearance, or biochemical activity. Final identification depends on special tests. Anton (1934) first introduced the rabbit conjunctival test as a unique reaction of the genus Listeria; this reaction is the production of a keratoconjunctivitis by gently swabbing a broth culture on the tarsal conjunctiva without breaking the mucosal surface. Julianelle (1941) amplified this work and verified the specificity of the reaction. He pointed out that specific local immunity usually follows recovery from this keratoconjunctivitis. The organisms isolated from the patients reported here showed the characteristic conjunctival reaction. Furthermore, identification is further established in the case of Listeria from Patient R. O. by the demonstration of local immunity in the rabbit to a subsequent inoculation with a known Listeria strain. Identification of Listeria strains may also be made serologically, using specific antiserum produced in animals with a known Listeria strain.

The development of agglutinins against Listeria in the serum of patients who have recovered from this infection is apparently inconstant, but such agglutinins have been found in a few instances. The agglutinin titer, when present, is usually low, but one of Kapsenberg's (1941) patients had a titer of 1:800 and Beute and co-workers (1948) found a titer of 1:600 in their case. In Patient R. O. only a very low titer of agglutinins was observed; the lack of agglutination of two other known Listerias suggests possible immunological differences between strains.

L. monocytogenes has a world-wide distribution in many animal hosts, including sheep, cattle, swine, goats, dogs, horses, chickens, canaries, rats, guinea pigs, foxes, and ferrets (Gray and co-workers, 1951; Norman and co-workers, 1951; Kaplan, 1945, and Girard and Murray, 1951). There appears to be no evidence that animals may serve as a reservoir of infection for humans.

The organism survives for long periods under various conditions with no loss of pathogenicity (Gray and co-workers, 1951).

The portal of entry of the organism in humans is obscure. There is some evidence that the nasal route is the probable pathway of natural infection in animals. Experi-

mentally, monkeys could not be infected intranasally and mice were infected via the gastrointestinal tract (Kaplan, 1945). The first patient reported here (R. O.) had respiratory symptoms for five days prior to the onset of meningeal symptoms and had physical signs and x-ray evidence of pneumonitis early in his course. The second patient reported (J. K.) had rales at the base of the left lung on admission. Stanley's (1948) patient had clinical pneumonia for three days.

Attempts to discover carriers of L. monocytogenes among human beings have been unsuccessful (Kaplan, 1945).

The sporadic nature of Listeria infections in man and animals indicates a low degree of communicability. On the other hand, Atkinson's (1917) five cases (organisms classed as diphtheroids) in children all occurred within a 13-day period. Burn (1936) reported two cases in infants born the same day in the visiting obstetric service of a hospital. Line and Cherry (1952) report two infants born in the same delivery room within two days of each other who were in the same nursery for 24 hours and whose mothers shared a common bath; these infants became sick within two days of each other. These instances suggest that it would be well to use isolation technique in Listeria meningitis.

The clinical picture is that of any suppurative meningitis with or without septicemia. Other findings vary but may include pneumonia or bronchiolitis, focal necrosis and patchy fatty degeneration of the liver, splenomegaly, otitis media, and mastoiditis. Foci of infection in the nasal accessory sinuses or mastoids apparently do not play an important role in Listeria meningitis; careful search revealed no evidence of such infection in Patient R. O. reported here, but Patient J. K. did have x-ray evidence of chronic maxillary sinusitis. The combination of pneumonitis and suppurative meningitis should suggest the possibility of Listerial infection.

Although some reviews state that the cells in the spinal fluids are predominantly lymphocytes, most of the reported cases show primarily polymorphonuclear leucocytes on the initial spinal tap. The case of Schultz and co-workers (1934) is a striking exception in showing 95% mononuclear cells on the first spinal tap, done on the third day of illness. Other laboratory findings are in line with findings in other types of meningitis. The urinary findings in the patients reported here are thought to be unrelated to the Listerial infection. It is interesting that both of the reported patients should have had a rather persistent low-grade leucocytosis and mild eosinophilia; this has not been reported before and could well have been coincidental and due to a drug reaction. Patient R. O. had a rash, which disappeared after treatment with diphenhydramine. Patients with Listerial meningitis do not develop antibodies for sheep red blood cells.

Only 5 of 23 untreated patients have recovered, and one of these was followed only a short period and had a residual hydrocephalus. In recent years the mortality in Listerial meningitis has been reduced considerably. Of nine patients treated with only sulfonamides or azosulfamide (Prontosil) or with a combination of sulfonamides and penicillin, only one has died; one had a possible residual hydrocephalus. Two patients were treated with sulfadiazine, penicillin, and streptomycin; one died (admitted one day before death) and the other recovered. Three other patients were treated with several agents, but the resulting cures were attributed to chlortetracycline and oxytetracycline, respectively, in two of these and to chlortetracycline, oxytetracycline, and chloramphenicol in the third (Line and Cherry, 1952; Bennett,

1952, and Line and Appleton, 1952); one of these three patients died nine months later, after surgery for a complicating hydrocephalus. The first patient reported here (R. O.) was also treated with several agents. He definitely became worse on penicillin and sulfonamide therapy, perhaps because of insufficient amounts of the drugs, in spite of the organism's moderate sensitivity to penicillin in vitro. He showed considerable improvement after two doses of 500 mg. of chlortetracycline intravenously. Although he received dihydrostreptomycin in addition subsequently, it is believed that the chlortetracycline played the decisive role. In the case of the second patient reported here (J. K.) it is difficult to attribute the successful recovery to any one drug, but the patient had shown some improvement during the first day, when he received only penicillin (in massive doses) plus one dose of sulfadiazine. It would appear that sulfadiazine, chlortetracycline, and oxytetracycline are all effective agents for the treatment of Listerial meningitis and that penicillin can also be effective but should probably be given in large doses, preferably by the intravenous route as well as intramuscularly.

Sensitivity studies have been done on only a few strains of Listeria. Stanley (1948) found his patient's strain sensitive to 0.31 units per cubic centimeter of penicillin and 6.25 $\gamma$ per cubic centimeter of streptomycin. Berry's (1950) strain was sensitive to 0.09 to 0.19 units per cubic centimeter of penicillin. Norman and co-workers (1951) tested three strains of Listeria with a modified turbidimetric procedure employing a 50% end-point; all three strains were sensitive to 0.83 $\gamma$ per cubic centimeter of chloramphenicol and 0.05 $\gamma$ per cubic centimeter of chlortetracycline. These authors found chlortetracycline more effective than chloramphenicol in the treatment of experimental Listeria infections in mice. Bennett and co-workers (1952) did tube-dilution sensitivity tests on the strain isolated from their case and obtained the following results: penicillin, 0.5 unit per cubic centimeter; streptomycin, 12.5 $\gamma$ per cubic centimeter; chlortetracycline, 0.37 $\gamma$ per cubic centimeter; oxytetracycline, 0.75 $\gamma$ per cubic centimeter, and chloramphenicol, 3.1 $\gamma$ per cubic centimeter. The sensitivity studies in the present report reveal remarkably consistent results in all six strains and suggest that several agents would be effective in the treatment of Listeria infections. Judging from these studies and the limited clinical experience available, the treatment of choice in Listerial meningitis would seem to be chlortetracycline or oxytetracycline—preferably intravenously for the first few days—in combination with sulfadiazine and/or streptomycin.

## SUMMARY

The literature on Listerial meningitis is reviewed and two new cases are reported with clinical data and laboratory studies; sensitivity studies with seven antibiotics on six strains of Listeria from human sources are reported. It is suggested that Listerial meningitis can be treated effectively with chlortetracycline (Aureomycin) or oxytetracycline (Terramycin) plus sulfadiazine and/or streptomycin.

## ADDENDUM

Since this manuscript was prepared, another case report has appeared in the literature (Binder, M. A.; Diehl, C.; Weiss, J., and Ray, H.: Listeria Meningitis, Ann. Int. Med. **38:** 1315, 1953).

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# EFFECTS OF ABDOMINAL DISTENTION BY ASCITES ON LUNG VOLUMES AND VENTILATION

W. H. ABELMANN, M.D.
N. R. FRANK, M.D.
E. A. GAENSLER, M.D.
AND
D. W. CUGELL, M.D.
BOSTON

ABDOMINAL distention may cause dyspnea in patients without disease of the heart or lungs and may aggravate dyspnea of patients with heart disease.* Reports of measurements of lung volumes and pulmonary ventilation in patients with distention of the abdomen are characterized by variability of methods, conditions of study, and results. Most previous observations were largely incidental and often were made on single cases.†

The present study was undertaken to determine the effects of abdominal distention by ascites on lung volumes and ventilatory function, to elucidate the mechanisms by which abdominal distention produces dyspnea, and to ascertain whether relief following reduction of distention is accompanied by measurable changes in pulmonary function.

## MATERIAL AND METHODS

*Selection of Patients.*—Thirteen patients with massive ascites were studied before and within 48 hours after paracentesis. In two of these patients (Cases 7 and 8) the studies were repeated when fluid had reaccumulated several months later and again after its removal. One patient (Case 10) was studied before treatment and after marked reduction of ascites during a regime of low-sodium diet and mercurial diuretics over a period of 10 days. Ascites was attributed to congestive heart failure in eight patients, to Laennec's cirrhosis in five, and to carcinomatosis in one.

The patients were arranged in three groups. Group I consisted of five patients with Laennec's cirrhosis and one patient with carcinomatosis; Group II comprised six patients with congestive heart failure; Group III consisted of two patients with heart failure who, in contrast to subjects in Groups I and II, had severe ventilatory insufficiency preceding formation of ascites.

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School; the Physiology Laboratory, Thoracic Surgery Service, Sanatorium Division of the Boston City Hospital, Mattapan, and the Department of Surgery, Boston University School of Medicine.

* References 1-7.

† References 1-9.

*Methods.*—Patients were studied in the postabsorptive state when possible, but no effort was made to achieve a basal state. A detailed outline of the routine ventilatory studies performed in this laboratory has been reported recently.‡ The resting minute ventilation, oxygen consumption, ventilatory equivalent for oxygen, and the vital capacity and its subdivisions were obtained by closed-circuit spirometry with the patients breathing oxygen-enriched gas in the supine position. Vital capacities were also determined in the upright position, the greatest of three efforts being recorded. A timing attachment was used to record the volume of air delivered during the first, first two, and first three seconds of the maximal expiratory effort.[12] The residual volume was determined by the open-circuit oxygen-breathing method of Darling and associates[13] with some modifications.[14] Determinations were made in duplicate, and the mean value was recorded. The maximum breathing capacity was determined during 15 or 30 seconds, using a high velocity respiratory valve and a Douglas bag.[15] This test was performed in duplicate or triplicate, the maximal effort being recorded. All gas volumes are reported at BTPS

TABLE 1.—*Ventilation and Lung Volumes, Group I: Ascites Secondary to Laennec's Cirrhosis (Cases 1 to 5) and Carcinomatosis (Case 6) Before and After Paracentesis*

| | Case 1 | | Case 2 | | Case 3 | | Case 4 | | Case 5 | | Case 6 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Before | After | Before | After | Before | After | Before | After | Before | After | Before | After |
| Age, yr. | 43 | | 53 | | 33 | | 59 | | 38 | | 80 | |
| Sex | F | | F | | M | | M | | F | | M | |
| BSA, m.²* | 1.74 | | 1.49 | | 1.75 | | 1.68 | | 1.52 | | 1.78 | |
| Ascitic fluid withdrawn, L. | 10 | | 2 | | 12 | | 8 | | 7 | | 10 | |
| Resp. rate | 19 | 16 | 22 | 20 | 16 | 14 | 16 | 17 | ... | ... | 19 | 16 |
| Tidal volume, cc. | 350 | 435 | 405 | 485 | 570 | 730 | 385 | 380 | ... | ... | 515 | 620 |
| Rest. ventil., L./min. | 6.57 | 6.93 | 9.10 | 9.69 | 9.12 | 9.96 | 6.16 | 6.46 | ... | ... | 9.75 | 9.62 |
| Oxygen uptake, cc./min. | 258 | 252 | 214 | 230 | 356 | 314 | 390 | 296 | ... | ... | 304 | 272 |
| Vent. equiv., L./100 cc. | 2.6 | 2.7 | 4.2 | 4.2 | 2.6 | 3.2 | 1.6 | 2.2 | ... | ... | 3.2 | 3.5 |
| Max. breath. cap., L./min. | 50 | 69 | ... | ... | 122 | 124 | 82 | 78 | 51 | 63 | 123 | ... |
| Upright vital cap., cc. | 1,340 | 2,030 | ... | ... | 3,420 | 3,230 | 1,830 | 2,800 | 1,750 | 1,920 | 3,290 | 3,200 |
| Inspiratory cap., cc. | 1,195 | 1,515 | 1,540 | 1,630 | 2,680 | 2,660 | 1,730 | 2,560 | ... | ... | 1,810 | 1,920 |
| Expir. reserve, cc. | 250 | 270 | 225 | 370 | 290 | 670 | 215 | 130 | ... | ... | 765 | 790 |
| Supine vital cap., cc. | 1,440 | 1,790 | 1,765 | 2,000 | 2,970 | 3,330 | 1,945 | 2,690 | ... | ... | 2,575 | 2,710 |
| Residual volume, cc. | 965 | 935 | 1,070 | 1,015 | 1,155 | 1,415 | 1,545 | 1,735 | ... | ... | ... | ... |
| Funct. resid. cap., cc. | 1,210 | 1,210 | 1,295 | 1,385 | 1,445 | 2,085 | 1,760 | 1,865 | ... | ... | ... | ... |
| Total lung cap., cc. | 2,405 | 2,725 | 2,835 | 3,015 | 4,125 | 4,745 | 3,490 | 4,425 | ... | ... | ... | ... |
| R. V./T. L. C. × 100, % | 40 | 34 | 39 | 34 | 28 | 30 | 44 | 39 | ... | ... | ... | ... |

* After paracentesis.

(body temperature, ambient pressure, and saturated with water vapor). Where results of pulmonary ventilation studies are reported as percentages of the predicted normal, the regression equations of Baldwin and associates were used for prediction.[16]

## RESULTS

The results for Groups I and II are discussed first; reported mean values are derived from these two groups only. Patients 13 and 14 (Group III), with ventilatory insufficiency preceding formation of ascites, were not comparable to the remaining patients.

*Lung Volumes.*—Individual measurements of lung volumes and their subdivisions before and after relief of ascites are enumerated in Tables 1 and 2 and summarized in Figure 1.

The vital capacity in the upright position was reduced in most patients with ascites and averaged 64% of the predicted. After paracentesis it increased in most patients, more in those who had shown the greatest impairment before

‡ References 10 and 11.

TABLE 2.—*Ventilation and Lung Volumes, Group II: Ascites Secondary to Congestive Heart Failure Before and After Paracentesis*

| | Case 7A | | Case 7B | | Case 8A | | Case 8B | | Case 9 | | Case 10 | | Case 11 | | Case 12 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Before | After | Before | After | Before | After | Before | After | Before | After | Before | After | Before | After | Before | After |
| Diagnosis | Rheum. H. D., Card. Cirrh. | | Rheum. H. D., Card. Cirrh. | | Rheum. H. D., Card. Cirrh. | | Rheum. H. D., Card. Cirrh. | | Rheum. H. D., Card. Cirrh. | | Arterio-scler. H. D. | | Arterio-scler. H. D. | | Arterio-scler. H. D. | |
| Age, yr. | 28 | | 28 | | 65 | | 65 | | 38 | | 57 | | 78 | | 58 | |
| Sex | M | | M | | F | | F | | F | | F | | M | | M | |
| BSA, m.²* | 1.56 | | 1.60 | | 1.60 | | 1.67 | | 1.45 | | 1.69 | | 1.87 | | 1.80 | |
| Ascitic fluid withdrawn, L. | 6 | | 8 | | 15 | | 14 | | 7 | | † | | 21 | | 7 | |
| Resp. rate | 12 | 8 | 10 | 7 | 16 | 16 | 20 | 16 | 20 | 21 | 26 | 21 | 13 | 16 | 19 | 17 |
| Tidal volume, cc. | 720 | 980 | 1,010 | 990 | 435 | 630 | 440 | 520 | 495 | 445 | 415 | 435 | 920 | 765 | 560 | 700 |
| Rest. Ventil., L./min. | 8.89 | 8.12 | 10.10 | 6.92 | 6.99 | 10.09 | 8.67 | 8.13 | 9.74 | 9.36 | 10.90 | 9.04 | 12.23 | 12.24 | 10.46 | 11.75 |
| Oxygen uptake, cc./min. | 321 | 302 | 337 | 274 | 289 | 272 | 344 | 254 | 270 | 269 | 332 | 294 | 284 | 268 | 328 | 352 |
| Ventil. equiv., L./100 cc. | 2.8 | 2.7 | 3.0 | 2.5 | 2.4 | 3.7 | 2.5 | 3.2 | 3.6 | 3.5 | 3.3 | 3.1 | 4.3 | 4.6 | 3.2 | 3.3 |
| Max. breath. capac., L./min. | 102 | 132 | 89 | 116 | 32 | 50 | ... | ... | 82 | 82 | 36 | 61 | 56 | 64 | 79 | 92 |
| Upright vital cap., cc. | 2,180 | 2,600 | 1,900 | 2,310 | 1,710 | 2,230 | ... | ... | 2,280 | 2,690 | 1,090 | 1,790 | 2,120 | 2,220 | 2,390 | 2,520 |
| Inspir. cap., cc. | 2,235 | 2,400 | 1,690 | 1,870 | 1,680 | 1,945 | 1,480 | 1,950 | 2,025 | 2,095 | 765 | 1,350 | 1,970 | 1,580 | 1,695 | 1,720 |
| Expir. Res., cc. | 205 | 385 | 220 | 470 | 365 | 325 | 315 | 385 | 570 | 715 | 270 | 255 | 475 | 1,070 | 615 | 675 |
| Supine vital cap., cc. | 2,440 | 2,785 | 1,910 | 2,340 | 2,040 | 2,270 | 1,790 | 2,335 | 2,595 | 2,810 | 1,040 | 1,605 | 2,445 | 2,650 | 2,310 | 1,395 |
| Residual volume, cc. | 1,480 | 1,555 | 1,260 | 1,090 | 1,060 | 1,440 | 1,140 | 1,165 | 1,220 | 1,335 | 880 | 1,175 | ... | ... | 1,930 | 1,905 |
| Funct. resid. cap., cc. | 1,685 | 1,940 | 1,475 | 1,560 | 1,425 | 1,765 | 1,455 | 1,550 | 1,790 | 2,055 | 1,155 | 1,430 | ... | ... | 2,550 | 2,580 |
| Total lung cap., cc. | 3,920 | 4,340 | 3,165 | 3,430 | 3,100 | 3,710 | 2,930 | 3,500 | 3,815 | 4,145 | 1,920 | 2,780 | ... | ... | 4,240 | 4,300 |
| R. V./T. L. C. × 100, % | 38 | 36 | 40 | 32 | 35 | 39 | 39 | 33 | 32 | 32 | 46 | 42 | ... | ... | 46 | 44 |

* After paracentesis.
† Ascites subsided under medical therapy. Studies repeated after loss of 5.5 kg. in 10 days.

paracentesis. In one patient with a normal vital capacity (Case 6) and in another with a slightly reduced capacity before paracentesis (Case 3) this volume decreased slightly afterwards. The mean increase after paracentesis was 18%. The inspiratory capacity after paracentesis increased by an average of 16%, while the expiratory reserve showed a mean increase of 41%.

The mean residual volume was 112% of predicted; after paracentesis it increased in seven patients and decreased in four. On the average it was 9% larger after paracentesis.

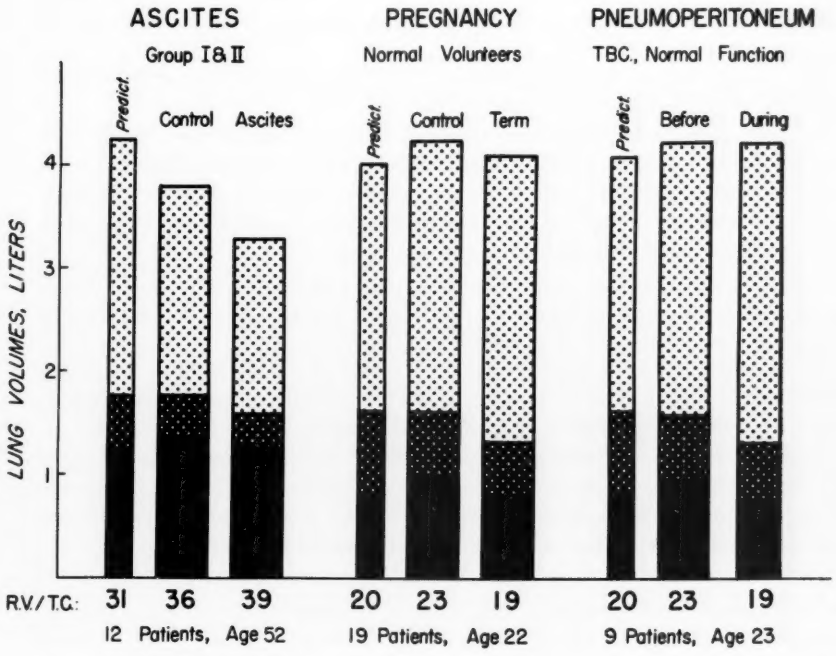


Fig. 1.—Effects of ascites, pregnancy, and pneumoperitoneum on lung volume compartments.

The total lung capacity for the group was 76% of the predicted volume at the time of initial study and increased in all 11 patients after paracentesis on the average by 16%. The mean total capacity was 88% of that predicted after treatment. The percentage of the total lung capacity occupied by residual volume was uniformly increased in patients with ascites and was affected variably by paracentesis, being decreased in eight patients, unchanged in one, and increased in two.

The functional residual capacity, a measure of the volume of the lungs in the "pulmonary resting position," averaged 89% of predicted in the presence of massive ascites and increased to 101% of predicted after withdrawal of fluid.

*Ventilation.*—Individual ventilatory measurements before and after relief from ascites are shown in Tables 1 and 2.

The respiratory rate in general was elevated at the time of initial study and usually decreased after paracentesis. Changes in the tidal volume were in direction opposite to the changes in respiratory rate. The mean tidal volume increased 15%. Resting ventilation showed no consistent change after paracentesis.

Resting oxygen consumption decreased in 9 of 13 instances after paracentesis, with a mean change of —4%. The ventilatory equivalent for oxygen was larger in eight and smaller in five instances, with a mean change of + 10%.

The index of intrapulmonary mixing was normal in all but one patient and showed no characteristic change after treatment. Patient 4 had an index of 2.8% before and 3.2% after paracentesis. This elevated index was associated with hypoventilation and the lowest minute volume and ventilatory equivalent for the group.

The timed vital capacities were comparable to those of convalescent hospital patients of similar age without pulmonary disease.[12]

In eight patients the maximum breathing capacity was reduced to 87% of predicted or less, and in every instance relief from ascites was followed by a significant increase of this volume. Three patients showed a normal or slightly decreased maximum breathing capacity despite marked ascites. In these three there was no significant change following paracentesis.

*Dyspnea and Breathing Reserve.*—Most of our patients with massive ascites experienced dyspnea on exertion and were limited in their activity. Shortness of breath was always lessened, if not abolished, by paracentesis.

The breathing reserve at rest [16] in the presence of massive ascites was below 90% in all but three instances (Cases 3, 4, and 7*A*). After paracentesis it increased in 7 of 10; the mean increase was 5% of the initial value.

In six patients the walking ventilation and walking dyspnea index were determined according to Warring [15] and were found elevated in all. After paracentesis the walking index decreased 29%, due both to a decrease in the walking ventilation and to an increase in the maximum breathing capacity.

*Group III.*—This group comprises two patients who developed severe ascites in the presence of pulmonary insufficiency due to far-advanced tuberculosis and subsequent collapse and resection. In both, pulmonary function prior to the development of ascites was known, and "control" values were therefore available.

The first patient (Case 13), a 28-year-old woman, entered the sanatorium with multiple cavities throughout the left lung. In spite of this, pulmonary function was within normal limits (Fig. 2). Because of a poor response to chemotherapy and pneumoperitoneum, a left pneumonectomy was performed five months later. Function was evaluated first at weekly and later at monthly intervals. The space in the left hemithorax was maintained by air refills and was later filled with a plastic sponge. Tuberculous empyema and ulceration of the bronchial stump required removal of the sponge and a staged thoracoplasty one year after resection. Shortly after this a pericardial friction rub was heard, the heart shadow enlarged, and ascites developed. As the amount of fluid increased function became severely impaired (Fig. 2). In spite of intensive medical therapy, paracentesis became necessary because of intolerable dyspnea at rest. At this time the maximum breathing capacity was 26 liters per minute, the vital capacity 660 cc., and the total lung capacity 1,200 cc. Relief was immediate, and six hours after removal of 18 liters of fluid both maximum breathing capacity and lung volumes had nearly doubled (Fig. 2). At the time of discharge, when medical therapy had been discontinued and all fluid had disappeared, a further slight improvement of function was measured.

The second patient (Case 14), a 30-year-old woman with bronchial asthma since childhood, had entered the sanatorium for the third time with far-advanced pulmonary tuberculosis, a right pneumothorax of five years' duration, and a giant cavity at the apex of the lower lobe of the left lung. Function was greatly impaired due to both restrictive and obstructive ventilatory insufficiency. A further reduction of function occurred after left cavernostomy, phrenic interruption, and pneumoperitoneum (Fig. 3). An extrapleural pneumothorax on the right was eventually required to close residual cavities. The patient was discharged five years after

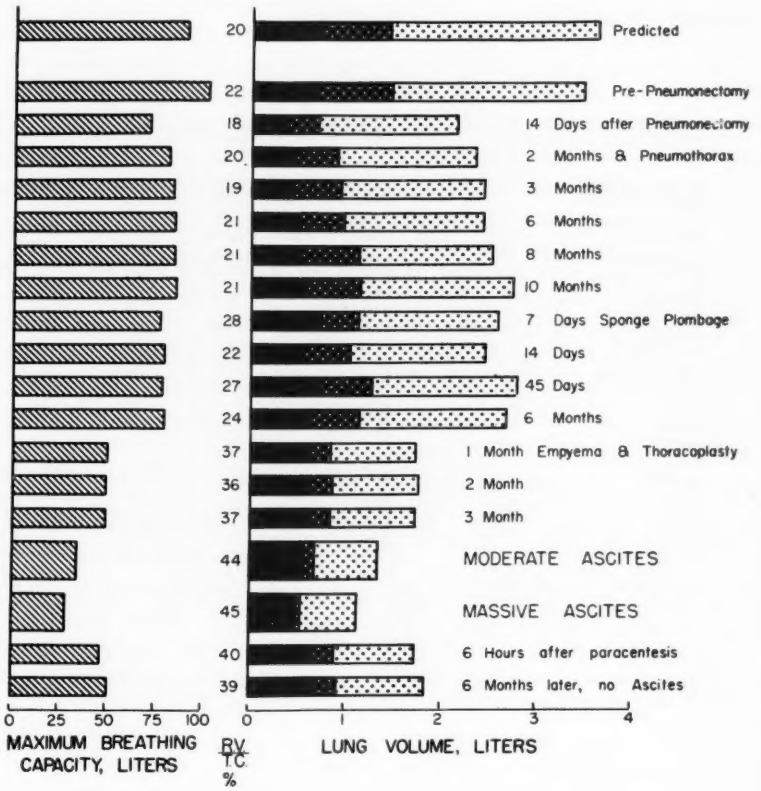


Fig. 2 (Case 13).—Ascites after pneumonectomy.

admission but had to be readmitted one year later during an asthmatic attack with severe dyspnea and marked cyanosis. She improved with bronchodilator drugs, but ascites developed and was accompanied by increasing dyspnea at rest. In spite of the usual medical therapy, right heart failure progressed and several paracenteses were required, primarily for the relief of dyspnea. With severe ascites the maximum breathing capacity was only 18 liters per minute, and it increased to 26 liters per minute immediately after paracentesis. The vital capacity improved from 650 to 1,020 cc. and the total lung capacity from 1,200 to 1,700 cc. Two months before death reaccumulation of fluid was accompanied by a parallel deterioration of function (Fig. 3). Cor pulmonale and its sequelae were the immediate cause of death.

In these patients the actual reduction of breathing capacity and lung volumes due to ascites was not larger than in the patients without preexisting pulmonary insufficiency. Because of the low initial values the decreases expressed as percent of total initial function were much greater and maximal performance in the presence of ascites much smaller. Paracentesis therefore caused much more striking subjective and objective improvement of breathing and, in fact, was necessitated only because of intolerable dyspnea at rest. Among other data, not shown in Figures 2 and 3, the most striking changes after paracentesis were a marked increase of tidal excursions and a fall of respiratory rate.

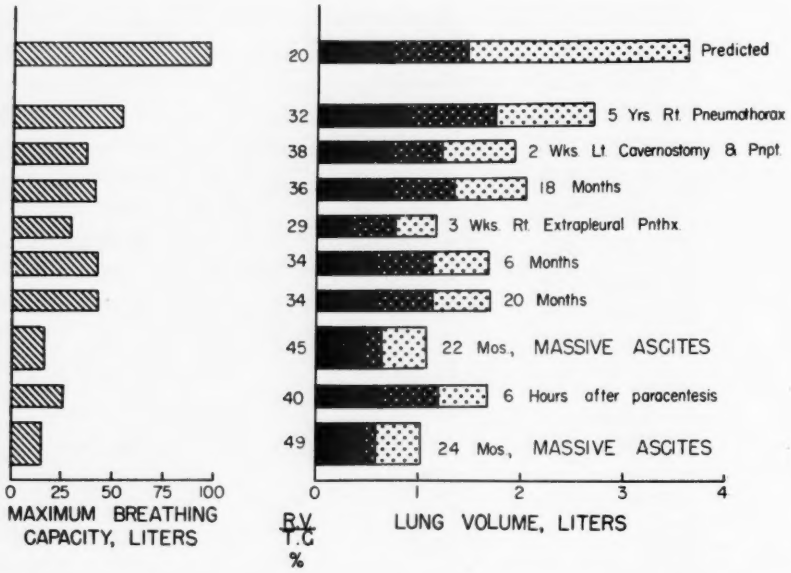
0 25 50 75 100
MAXIMUM BREATHING CAPACITY, LITERS
20 Predicted
32 5 Yrs. Rt. Pneumothorax
38 2 Wks. Lt. Cavernostomy & Pnpt.
36 18 Months
29 3 Wks. Rt. Extrapleural Pnthx.
34 6 Months
34 20 Months
45 22 Mos., MASSIVE ASCITES
40 6 Hours after paracentesis
49 24 Mos., MASSIVE ASCITES
0 1 2 3 4
RV / TC %
LUNG VOLUME, LITERS

Fig. 3 (Case 14).—Ascites after intrapleural and extrapleural pneumothorax, cavernostomy, phrenic paralysis, and pneumoperitoneum in a patient with bronchial asthma.

COMMENT

*Effects of Ascites on Lung Volume and Function.*—Patients with severe ascites usually have rapid and shallow respirations. This clinical observation was confirmed by our studies. After paracentesis the respiratory rate tended to decrease and the tidal volume to increase. Since minute ventilation showed no consistent change, the ratio of alveolar to dead space ventilation tended to improve. From percussion and fluoroscopic examination it is well known that ascites is accompanied by an elevation and by decreased maximal excursion of the diaphragm. Correspondingly, the divisions of the lung volume were found generally diminished. The reduction in the vital capacity was caused by a decrease in both of its components, the inspiratory capacity and the expiratory reserve. The slight but definite decrease in the residual volume occurring together with a marked decrease in the expiratory

reserve resulted in a decrease of the functional residual capacity. This smaller volume of the lungs in the "resting midposition" could be interpreted as a pulmonary collapse of 11%. These findings are in essential agreement with previous studies.§

The changes in lung volumes have been attributed to the increase in intraperitoneal pressure effected by abdominal distention which is transmitted to the chest, causing an increase of the mean intrapleural pressure. This has been demonstrated by Frey in rabbits and dogs [17] and by Prinzmetal and Kountz in a patient with ascites secondary to cirrhosis.[18] In animal studies, Frey has shown that as the abdominal pressure is raised the respiratory rate increases and that this response fails to occur after section of the vagi in the neck.[17] It appears likely that the Hering-Breuer reflex plays a role in the increased respiratory rate of patients whose lungs are partially deflated by abdominal distention.

Increased intra-abdominal pressure results not only in an elevation of the diaphragm but also in distention and increased rigidity of the abdominal wall and relative fixation of the diaphragm. Thus the system comprising the diaphragm, the abdominal contents, and the abdominal wall is rendered stiffer. Because this system forms part of the functional thoracic cage, the over-all elasticity of the thoracic cage is affected: the chest becomes more rigid. Movements of a more rigid thoracic cage require additional amounts of energy, and the work of breathing is increased. In the resting state the work of breathing is small and the increase in oxygen consumption associated with ascites is probably only partly attributable to the increased work of breathing. During effort, however, the work of breathing becomes considerable.

The decrease in the maximum breathing capacity in the presence of ascites appears to be due not only to the decrease in lung volumes but also to the increased resistance and fixation of the diaphragm and abdominal wall. This seems the more plausible since patients with pure restrictive ventilatory insufficiency not infrequently show little decrease in maximum breathing capacity.[19]

*Lung Volumes and Function After Paracentesis.*—After removal of most of the fluid, the total lung capacity, vital capacity, and maximum breathing capacity did not always reach the predicted normal value for the patient (Fig. 1). Even after treatment the mean vital capacity for the entire group was only 78% and the mean total lung capacity only 88% of the predicted. The residual volume, on the other hand, averaged 112% of the predicted value in Group I and 125% in Group II. The maximum breathing capacity was only 89% for both groups.

Several factors may be responsible for this remaining ventilatory insufficiency after removal of ascitic fluid. All patients studied were quite ill and weak even after relief from abdominal distention. The abdominal wall, very relaxed after paracentesis, probably did not participate effectively in the maximal expiratory effort. This may have been augmented by discomfort at the site of paracentesis. It was not always possible to remove all fluid. Residual ascites in some cases may have limited pulmonary function. These factors may have played a role in both Groups I and II. Pulmonary congestion was an added factor in Group II. The large residual volume in Group II is not surprising and reflects the increased rigidity of the lungs as seen in patients with mitral stenosis.[19] In Group I only

§ References 1-3 and 7-9.

Patient 3 had a definitely enlarged residual volume. This patient had ascites secondary to Laennec's cirrhosis but also had mitral stenosis, which may explain his residual volume of 137% of predicted.

Ventilatory function may well show further improvement several days after paracentesis, as the puncture wound heals, the abdominal wall regains its tone, and the patient regains strength. Patient 3, who was studied immediately after paracentesis and again six days later, showed a further increase in vital capacity of 515 cc. at the later date.

*Comparison of the Effects of Ascites, Pneumoperitoneum, and Pregnancy on Pulmonary Function.*—Among the conditions which increase intraperitoneal pressure, pregnancy and therapeutic pneumoperitoneum are seen more often than ascites. The effects of these conditions upon pulmonary function have previously been investigated in our laboratory, using the same methods as in the present

TABLE 3.—*Comparison of the Effects of Ascites, Pneumoperitoneum, and Pregnancy upon Lung Volumes and Ventilation*

| | Ascites, Groups I and II | | | Pneumoperitoneum, "Normal" Lungs | | | Pregnancy, Normal Volunteers | | |
|---|---|---|---|---|---|---|---|---|---|
| | Control | Ascites | % Change | Before | During | % Change | Control | Term | % Change |
| Patients, no. | 12 | 12 | .... | 9 | 9 | .... | 19 | 19 | .... |
| Age, yr. | 52 | 52 | .... | 23 | 23 | .... | 22 | 22 | .... |
| Respiratory rate | 16 | 18 | +14 | 12 | 12 | 0 | 15 | 16 | +10 |
| Tidal volume, cc. | 624 | 555 | −11 | 585 | 548 | − 6 | 487 | 678 | +39 |
| Resting ventilation, L. | 9.10 | 9.13 | + 2 | 7.02 | 6.57 | − 6 | 7.27 | 10.34 | +42 |
| Resting oxygen uptake, cc. | 281 | 310 | + 5 | 237 | 225 | − 5 | 201 | 266 | +32 |
| Ventil. equiv., L./100 cc. | 3.3 | 3.0 | − 7 | 2.5 | 2.4 | − 3 | 3.0 | 3.3 | +10 |
| Max. breath. capac., L./min. | 85 | 71 | −18 | 95 | 106 | +12 | 102 | 96 | − 6 |
| Upright vital capac., cc. | 2,460 | 2,110 | −11 | 3,174 | 3,158 | 0 | 3,200 | 3,140 | − 2 |
| Inspiratory capacity, cc. | 1,940 | 1,730 | −12 | 2,619 | 2,859 | + 9 | 2,625 | 2,745 | + 5 |
| Expiratory reserve, cc. | 500 | 370 | −17 | 631 | 519 | −18 | 655 | 555 | −15 |
| Supine vital capacity, cc. | 2,440 | 2,095 | −15 | 3,250 | 3,378 | + 4 | 3,280 | 3,300 | + 1 |
| Residual volume, cc. | 1,340 | 1,245 | − 6 | 944 | 781 | −17 | 965 | 770 | −20 |
| Funct. resid. capac., cc. | 1,765 | 1,570 | −11 | 1,575 | 1,300 | −17 | 1,620 | 1,325 | −18 |
| Total lung capacity, cc. | 3,740 | 3,270 | −13 | 4,194 | 4,186 | − 1 | 4,245 | 4,070 | − 4 |
| R. V./T. L. C. × 100, % | 36 | 39 | + 8 | 23 | 19 | −17 | 23 | 19 | −17 |

study. Nineteen healthy young women were studied when not pregnant and throughout pregnancy.[11] Nine young women with minimal pulmonary tuberculosis but functionally normal lungs were studied before and some time after induction of pneumoperitoneum.[20] The mean values and changes produced by ascites, pneumoperitoneum, and pregnancy are compared in Table 3 and in Figure 1. The latter two groups of subjects were comparable to each other, whereas the patients with ascites were generally older and predominantly male. In young women, pneumoperitoneum and pregnancy caused identical changes in lung volumes, characterized by reduction of the functional residual capacity of 17 and 18%, respectively. This pulmonary collapse was somewhat larger than that observed as the result of ascites. In pneumoperitoneum and pregnancy the pulmonary collapse was effected by proportionally equal reductions of the residual volume and expiratory reserve, while ascites caused a comparable decrease in the expiratory reserve but a relatively smaller decrease in the residual volume. The difference may have been due to the more advanced age of the patients with ascites and the inclusion of subjects with mitral stenosis. It must also be noted that

the "control" studies of the ascites group were not performed before the advent of ascites, while in the other two groups studies were possible with the patients in the "normal" state. In pneumoperitoneum and in pregnancy the reduction of the functional residual capacity was offset by an increase of the inspiratory capacity, with the total lung capacity remaining unchanged. Ascites was accompanied by a marked reduction of both inspiratory capacity and total lung capacity. This difference may have been due to a relatively greater increase in intra-abdominal pressure by massive ascites than by pregnancy or conventional pneumoperitoneum. The average volume of ascitic fluid withdrawn was 10 liters, the maximum 21 liters. Thus, in some patients the volume of ascites was considerably greater than the volume of a pregnant uterus at term or of an established pneumoperitoneum.

Pregnancy was accompanied by marked hyperventilation, only partly accounted for by increased demand for oxygen. Pneumoperitoneum was not accompanied by significant changes in oxygen consumption or resting ventilation. The patients with ascites tended to have an increased oxygen consumption without an increase of resting ventilation.

The maximum breathing capacity increased slightly with pneumoperitoneum, decreased slightly during pregnancy, but decreased markedly in the presence of massive ascites. Again, it is suspected that these differences were related to the magnitude of abdominal distention and the compressibility of the abdominal contents.

*Clinical Considerations.*—Any attempt to account for the dyspnea experienced by patients with massive ascites must consider factors related to the underlying chronic disease process as well as factors brought into play by abdominal distention itself. In our patients with congestive heart failure dyspnea preceded the accumulation of ascites, was aggravated when ascites became severe, and decreased but did not subside after paracentesis. The patients with cirrhosis developed dyspnea only when abdominal distention became severe and were relieved of this symptom after paracentesis. The factors involved in the production of dyspnea have recently been reviewed by Richards.[21] He distinguishes three major influences: factors which restrict breathing by reducing ventilatory capacity, factors which render breathing labored by increasing ventilatory work, and stimuli to increased respiration resulting in hyperventilation. Factors belonging to all three of these categories appear involved in producing dyspnea in the presence of massive ascites. The reduction of the vital capacity results in a moderate restrictive ventilatory insufficiency, with a slight reduction of the breathing reserve at rest and a further reduction during mild exercise. Ventilatory work may be increased as the diaphragm and abdominal wall become more rigid. Partial deflation of the lungs conceivably could reflexly increase the respiratory rate.[17] However, neither pregnancy nor pneumothorax result in a significant increase in respiratory rate.

*Pulmonary Atelectasis and Infection.*—The reduction of the vital capacity together with the changes in the abdominal wall and diaphragm result in impaired tussive force, especially in persons weakened by chronic disease. Reduced effectiveness of cough together with pulmonary collapse favor accumulation of bronchial secretions, pulmonary infection, and atelectasis.‖ Indeed, plate-like basal atelectasis is frequently associated with immobilization and elevation of the diaphragm secondary to increased intraperitoneal pressure.[24] This was evident on the initial

roentgenograms of several of our patients. Bronchopneumonic infections in patients with massive ascites are also not infrequent. While reduction of the functional residual capacity of the magnitude observed in our patients may be well tolerated by healthy persons,¶ in bedridden severely ill patients it may constitute a factor predisposing to pulmonary atelectasis and infection.

*Treatment of Ascites.*—With increasing knowledge of the pathologic physiology of the development of ascites, paracentesis, long the standard treatment of ascites, is being replaced more and more by medical regimens effecting diuresis by rest, diets low in sodium, diuretics, and ion-exchange resins.# Such regimens represent progress in therapy, especially when they are directed at the prevention of retention of fluid. Also, paracentesis in patients with advanced cirrhosis is not without danger. Nelson and associates have drawn attention to hyponatremia following paracentesis.[30] Hepatic coma has been observed after paracentesis.* In view of this trend away from paracentesis it may be well to draw attention to the effects of severe ascites on the respiratory system described in the present study. In planning a course of therapy for the patient with ascites, the discomfort and possible harmful effects of the pulmonary collapse, ventilatory insufficiency, and decreased effectiveness of cough resulting from increased intra-abdominal pressure must not be neglected. This is especially important in the treatment of patients with ascites secondary to cirrhosis, in whom the response to diets low in sodium and to diuretics may be rather slow. These considerations are also important in patients with ascites who have complicating pulmonary insufficiency due to other causes. The present study demonstrates how rapidly paracentesis is followed by relief of dyspnea, expansion of the relatively collapsed lung, and increase of the breathing reserve.

## SUMMARY

Lung volumes and pulmonary ventilation were studied in 14 patients before and after relief from ascites. Distention of the abdomen by massive ascites resulted in ventilatory insufficiency of moderate degree, characterized by a reduction in the total lung capacity and its subdivisions and a decrease in maximum breathing capacity and breathing reserve. Massive ascites produced a mean collapse of the lungs in the resting position of 11% and a mean decrease in the vital capacity of 15%. The mean decrease in maximum breathing capacity was 18%.

The effects of ascites are compared to previously studied changes during pregnancy and during treatment with pneumoperitoneum. Although the decrease of the functional residual capacity due to ascites was generally less marked than that observed during pneumoperitoneum treatment and in pregnancy at term, the reductions in the vital capacity, total lung capacity, and maximum breathing capacity were much more severe.

The dyspnea occurring in patients with ascites is discussed in relation to these findings. The possible relationship of ascites to intercurrent pulmonary complications is considered. The therapeutic implications of paracentesis are discussed.

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¶ References 11 and 20.

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# TOXICITY OF ISONICOTINIC ACID HYDRAZIDES IN PULMONARY TUBERCULOSIS

## Toxicity of Isoniazid and Iproniazid Used Alone and in Combination with Streptomycin or *p*-Aminosalicylic Acid

E. O. COATES Jr., M.D.
G. L. BRICKMAN, M.D.
AND
G. M. MEADE, M.D.
TRUDEAU, N. Y.

INFORMATION available at the present time concerning the toxicity of isoniazid (isonicotinic acid hydrazide) has shown it to be a relatively safe agent for the treatment of pulmonary tuberculosis.* Although a variety of side-effects have been observed, the majority of these have been of minor importance. However, several reports have drawn attention to occasional severe reactions, in particular, psychoses,† peripheral neuritis,‡ hemoptyses,[6] and pellagra.[7] Furthermore, experience with iproniazid has shown it to be considerably more toxic than isoniazid.[1]

At Trudeau Sanatorium the use of iproniazid for investigation has recently been terminated because of frequent and sometimes severe side-effects, as compared to those observed with isoniazid. Documentation of the specific toxicity observed with each of these drugs, both alone and in combination with streptomycin or *p*-aminosalicylic acid (PAS), is important for comparison with present and future chemotherapeutic agents. This report presents data on the incidence of side-effects and causes of termination of therapy among a group of patients most of whom have received treatment with these agents for six months or more.

### MATERIAL AND METHODS

The data presented here summarize observations from a cooperative study group treated with isoniazid or iproniazid alone, followed by those from a smaller group treated with isoniazid or iproniazid in combination with streptomycin or PAS.§

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Isoniazid (Rimifon) and iproniazid (Marsilid) for this study were kindly supplied by Hoffmann-LaRoche, Inc., through the courtesy of Dr. Elmer Sevringhaus, Director of Clinical Research.

From the Trudeau Sanatorium, Assistant Medical Director (Dr. Coates), Medical Director (Dr. Meade), and Wunderley Traveling Scholar of the Royal Australasian College of Physicians (Dr. Brinkman).

* References 1, 2, and 3.

† References 1, 4, and 5.

‡ Reference 1 and Gammon, G.: Personal communication to the authors.

§ The following institutions and physicians contributed to this study: Ray Brook State Tuberculosis Hospital, Director, Dr. Frederick Beck; Sanatorium Gabriels, Director, Dr. John N. Hayes; Stony Wold Sanatorium, Director, Dr. Wayne Henning; Will Rogers Variety Clubs Hospital, Directors, Drs. George Wilson and Homer McCreary; and Drs. John N. Hayes, Henry W. Leetch, H. Frazer Parry, Francis B. Trudeau, and Charles Trembley, Saranac Lake, N. Y.

Patients receiving chemotherapy may be divided into four categories, as follows:

| | |
|---|---|
| 1. Iproniazid alone | 19 |
| 2. Iproniazid plus streptomycin | 16 |
| Iproniazid plus PAS | 7 |
| Total, iproniazid plus streptomycin or PAS | 23 |
| 3. Isoniazid alone | 27 |
| 4. Isoniazid plus streptomycin | 5 |
| Isoniazid plus PAS | 3 |
| Total, isoniazid plus streptomycin or PAS | 8 |
| Total patients | 77 |

Iproniazid was used in preference to isoniazid for the majority of patients on combined therapy because one of the aims of the investigation was determination of the usefulness of this derivative.

Only patients with active pulmonary tuberculosis were included in the study. None had previously received isonicotinic acid hydrazides; the majority on combined treatment took both drugs for the first time. A standard dose of 4 mg. per kilogram was employed for both isoniazid and iproniazid. The dosage of streptomycin was 1 gm. daily or 1 gm. twice a week; that of PAS, 12 gm. daily of free acid, or its equivalent of the sodium salt.

The duration of chemotherapy among the entire group of 77 patients was as follows:

| | |
|---|---|
| Discontinued because of toxicity after 4 to 26 weeks of therapy (average 8 weeks) | 14 |
| Treated for less than 6 months (range 2 to 6 months) then discontinued for reasons other than toxicity | 22 |
| (Many of these were removed from the study after a change of chemotherapy following treatment with isoniazid or iproniazid alone) | |
| Therapy for a minimum of 6 months | 41 |
| Total patients | 77 |

All persons were carefully checked for signs of toxicity at least once every week during therapy.

## CLINICAL OBSERVATIONS

The toxic reactions observed in these patients were similar in most respects to those during therapy of shorter duration, as previously reported.|| They may be divided into two main categories. In the first are certain effects apparently related to the autonomic nervous system, as follows:

*Constipation.*—Usually mild and readily controlled by gentle laxatives.

*Postural Hypotension.*—This was commonly severe enough to produce marked dizziness on standing. Several patients with this complaint had falls and narrowly escaped injury. Blood pressure levels, which were checked in the sitting and standing position for most of those on combined therapy, showed postural hypotension regularly present among those complaining of dizziness.

*Dryness of the Mouth.*—A definite, but minor complaint.

*Urinary Difficulties.*—Inability or delay in the initiation of micturition and occasional frequency and nocturia.

*Sweating.*—When present, this involved almost solely the head, neck, and upper chest.

*Impotence.*—Appeared clearly related to use of the drug in a few instances.

|| References 3 and 8.

*Bradycardia.*—Reduction of the pulse rate to 44 to 60 per minute in a few patients.

*Increasing Dyspnea.*—In some instances at least, this appeared to be related to bronchospasm, as evidenced by the presence of wheezing where none had been noted before. In one person given isoniazid repeated attacks of wheezing necessitated termination of therapy.

The second category consists of certain effects apparently related to the central nervous system and to the peripheral nerves. These are listed as follows:

*Mental Changes.*—Among those taking iproniazid, particularly when combined with streptomycin or PAS, "mental changes," in the broad use of the term, were the most serious form of toxicity. The following abnormalities were observed: (1) euphoria; (2) depression; (3) loss of memory; (4) terrifying nightmares; (5) inability to concentrate; (6) personality changes characterized by belligerence, aggressiveness, hyperactivity; (7) visual and auditory hallucinations; (8) agitation, paranoid psychosis. Restoration to the normal state generally occurred within 1 to 2 weeks after discontinuance of the drug.

*"Muscular Irritability."*—This is a descriptive term used to include various manifestations of increased motor activity, such as hyperreflexia, tremors, jerks, and twitching of the muscles of the extremities. These phenomena, particularly that of hyperreflexia, were the most constant concomitants of iproniazid therapy and, to considerably lesser degree, also of isoniazid therapy.

*Paresthesias.*—These included instances of numbness, tingling, or stiffness of the fingers or toes, as well as two cases of signs of peripheral neuritis.

Mention should also be made of a third group of miscellaneous side-effects. Purpuric skin rash, accompanied by a moderate hemoptysis, occurred in one person receiving isoniazid and in two patients taking iproniazid in combination with streptomycin. An increased incidence of hemoptyses during isoniazid therapy has been previously reported.[6]

Diplopia of moderate severity was a transient phenomenon in one patient receiving iproniazid and PAS.

Two instances of possible drug incompatibility were observed. One patient receiving iproniazid was given 100 mg. of meperidine hydrochloride (Demerol) hypodermically for gastrointestinal pain, during the fifth week of chemotherapy, after having taken this medication without incident several times prior to iproniazid treatment. The injection was followed within 20 minutes by a severe tetanic muscular spasm lasting for approximately 12 hours and accompanied initially by a shock-like state. However, one patient on isoniazid received meperidine regularly during therapy without untoward effects.

A second patient experienced convulsive muscular jerking following the administration of synthetic racemic epinephrine hydrochloride (Vaponefrin) by inhalation. Other patients have tolerated this medication without incident during therapy.

One fatality occurred during iproniazid therapy, the details of which are as follows: A 50-year-old man in good clinical condition, with moderately advanced pulmonary tuberculosis, was treated with iproniazid in the standard dosage of 4 mg. per kilogram. After 10 days of therapy, with only minor side-effects, sudden death occurred without warning. At autopsy no ascertainable cause of death could be found, but the hypothesis that it was caused by a ventricular fibrillation related to iproniazid must be considered.

*Onset and Duration of Side-Effects.*—Reactions to both isoniazid and iproniazid generally appeared within the first to the eighth week of therapy. In the present group, 60 to 70% of reactions occurred during the first month and 80 to 90% had appeared by the end of the second month of therapy. Amelioration or disappearance of side-effects was the general rule after the eighth treatment week among those who were still on therapy at this time.

*"Withdrawal" Syndrome.*—Selikoff and his co-workers have reported a series of "withdrawal" symptoms, similar to those encountered during initiation of therapy, following abrupt termination of treatment with iproniazid or isoniazid.¶ Such symptoms have recently been observed by us in 9 (64%) of 14 patients whose medication was abruptly changed to isoniazid after one to eight months on iproniazid treatment. The chief symptoms observed were nightmares, muscular

TABLE 1.—*Side-Effects During Therapy with Iproniazid and Isoniazid*

| Side-Effects | Iproniazid (19 Patients) | | Isoniazid (27 Patients) | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Autonomic | | | | |
| Constipation | 3 | 16 | 3 | 11 |
| Dizziness and/or hypotension | 10 | 53 | 8 | 30 |
| Urinary difficulties | 5 | 26 | 4 | 15 |
| Dryness of mouth | 2 | 11 | 4 | 15 |
| Sweating | 3 | 16 | 1 | 4 |
| Impotence | 1 | 5 | 0 | 0 |
| Bradycardia | 0 | 0 | 0 | 0 |
| Increasing dyspnea | 1 | 5 | 2 | 7 |
| CNS & peripheral nerves | | | | |
| Mental changes | 7 | 37 | 1 | 4 |
| Muscular irritability | 12 | 63 | 9 | 33 |
| Paresthesias | 4 | 21 | 3 | 11 |
| Miscellaneous | | | | |
| Edema | 3 | 16 | 0 | 0 |
| Purpura and hemoptysis | 0 | 0 | 1 | 4 |
| Reaction assoc. with meperidine | 1 | 5 | 0 | 0 |
| Reaction assoc. with racemic epinephrine | 0 | 0 | 1 | 4 |

twitchings, and difficulty with micturition, all gradually disappearing over a three-week interval. In five of the nine patients, all of whom had noticed some increased appetite during therapy, substitution of isoniazid for iproniazid was followed immediately by a marked diminution of appetite, which persisted thereafter.

*Incidence of Side-Effects.*—The incidence of side-effects among the 19 patients on iproniazid and the 27 on isoniazid used alone are tabulated in Table 1. Although the qualitative effects of the two drugs were similar, iproniazid was clearly more toxic than isoniazid, as previously noted by other observers.# This point is demonstrated by the higher incidence of muscular irritability (63% vs. 33%), dizziness (53% vs. 30%), mental changes (37% vs. 4%), and urinary difficulties (26% vs. 15%) among those on iproniazid.

Table 2 lists the side-effects obtained in the combined-therapy group. No separate figures are presented for those receiving hydrazide plus streptomycin versus those on hydrazide plus PAS, since the numbers involved were too small and the

¶ References 1 and 11.

# References 1 and 8.

results appeared to be essentially similar with both combinations. Again, reactions among those taking iproniazid were more common than among those on isoniazid and, in addition, appeared to be more frequent and more severe among those on combined treatment than among those on the single drug. This is illustrated, in particular, by the comparative percentages in the groups of those given iproniazid combined versus those given iproniazid alone (Table 2 compared to Table 1) of mental changes (57% vs. 37%), muscular irritability (87% vs. 63%), and urinary difficulties (57% vs. 26%).

When the severity of side-effects is considered, a more clear-cut difference is found between those receiving iproniazid alone and those receiving iproniazid plus streptomycin or PAS. Termination of therapy because of toxicity was necessary

TABLE 2.—*Side-Effects During Therapy with Iproniazid and Isoniazid Combined With Streptomycin or PAS*

| Side-Effects | Iproniazid + SM or PAS (23) * | | Isoniazid + SM or PAS (8) * | |
|---|---|---|---|---|
| | No. | % | No. | % |
| **Autonomic** | | | | |
| Constipation | 9 | 39 | 3 | 38 |
| Dizziness and/or hypotension | 13 | 57 | 4 | 50 |
| Urinary difficulties | 13 | 57 | 0 | 0 |
| Mouth dryness | 5 | 22 | 1 | 13 |
| Sweating | 7 | 30 | 0 | 0 |
| Impotence | 5 | 22 | 0 | 0 |
| Bradycardia | 3 | 13 | 0 | 0 |
| Increased dyspnea | 5 | 22 | 0 | 0 |
| **CNS & Peripheral Nerves** | | | | |
| Mental changes | 13 | 57 | 0 | 0 |
| Muscular irritability | 20 | 87 | 3 | 38 |
| Paresthesias | 5 | 22 | 2 | 26 |
| **Miscellaneous** | | | | |
| Edema | 3 | 13 | 1 | 13 |
| Purpura with hemoptysis | 2 | 9 | 0 | 0 |
| Diplopia | 1 | 4 | 0 | 0 |

* SM, streptomycin; PAS, *p*-aminosalicylic acid. The number of patients in each treatment group is given in parentheses.

in 9 (39%) of 23 on combined treatment compared with only 4 (21%) such cases among 19 taking iproniazid alone. Reduction of dosage or interruption of therapy was prescribed for an additional three patients in each of these groups. Thus, some form of alteration of therapy became necessary in 52% of those taking iproniazid in combination compared with 37% of those receiving iproniazid alone. These data are summarized in Table 3.

Among those receiving isoniazid, chemotherapy was terminated for only one patient (3%) and interrupted temporarily for two others, one of these being on isoniazid alone and one on isoniazid plus PAS. Insufficient numbers are available, however, for a statement on the incidence of side-effects among those receiving isoniazid in the combined-therapy versus those in the noncombined-therapy group.

The causes of termination of therapy in each group are listed in Table 4. Among those receiving iproniazid alone, therapy was discontinued in four, each of whom deserves special comment.

The first of these was a 42-year-old man with advanced pulmonary tuberculosis, whose chemotherapy was terminated during the sixth week because of recurring

severe muscle twitching and spasms, associated with increasing dyspnea and edema. The latter symptoms were believed to result largely from right-sided heart failure, but enhancement by the medication is a possibility.

The second termination of therapy under iproniazid alone, using the standard dosage of 4 mg. per kilogram, was precipitated by the gradual development of a severe quadrilateral peripheral neuropathy in a 40-year-old woman who had wide-

TABLE 3.—*Incidence of Termination, Interruption, or Reduction of Dosage Because of Drug Toxicity During Therapy with Iproniazid or Isoniazid*

| | Iproniazid (19) * | | Iproniazid + SM or PAS (23) * | | Whole Group on Iproniazid (42) * | | Isoniazid (27) * | | Isoniazid + SM or PAS (8) * | | Whole Group on Isoniazid (35) * | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % |
| Termination of therapy.. | 4 | 21 | 9 | 39 | 13 | 31 | 1 | 4 | 0 | 0 | 1 | 3 |
| Interruption of therapy or reduction of dosage..... | 3 | 16 | 3 | 13 | 6 | 14 | 1 | 4 | 1 | 13 | 2 | 6 |
| Totals ..... | 7 | 37 | 12 | 52 | 19 | 45 | 2 | 8 | 1 | 13 | 3 | 9 |

* SM, streptomycin; PAS, *p*-aminosalicylic acid. The number of patients in each treatment group is given in parentheses.

TABLE 4.—*Causes of Termination, Interruption, or Reduction of Dosage During Iproniazid and Isoniazid Therapy, Number of Patients*

| | Iproniazid | Iproniazid + SM or PAS * | Isoniazid (Whole Group) | Whole Group on INH * |
|---|---|---|---|---|
| Causes of termination of therapy: | | | | |
| Mental changes ..... | 1 | 6 | 0 | 7 |
| Muscular irritability ..... | 1 | 0 | 0 | 1 |
| Peripheral neuropathy ..... | 1 | 0 | 0 | 1 |
| Dizziness and/or hypotension..... | 0 | 2 | 0 | 2 |
| Increasing dyspnea ..... | 0 | 0 | 1 | 1 |
| Urinary difficulties ..... | 0 | 1 | 0 | 1 |
| Encephalitis ..... | 1 | 0 | 0 | 1 |
| Totals ..... | 4 | 9 | 1 | 14 |
| Causes of interruption or reduction of dosage (without termination of therapy) | | | | |
| Muscular irritability ..... | 3 | 0 | 0 | 3 |
| Urinary difficulties ..... | 0 | 1 | 0 | 1 |
| Bradycardia ..... | 0 | 1 | 0 | 1 |
| Increasing dyspnea ..... | 0 | 1 | 0 | 1 |
| Purpura and hemoptysis..... | 0 | 0 | 1 | 1 |
| Totals ..... | 3 | 3 | 1 | 7 |

* SM, streptomycin; PAS, *p*-aminosalicylic acid; INH, isonicotinic hydrazides.

spread metastases from an original carcinoma of the breast as well as active pulmonary tuberculosis. During the six months following cessation of iproniazid therapy the signs and symptoms became more severe in all four extremities in spite of strenuous therapy with a variety of agents. During the past 2 months, now approximately 10 months after termination of drug treatment, some slow but definite improvement is manifest. A few similar cases with high-dosage isoniazid treatment have been observed by another investigator during the past year.*

* Gammon, G.: Personal communication to the authors.

In a third case iproniazid treatment was terminated during the 15th week because of development of an agitated paranoid state requiring commitment to a mental institution. Recovery appeared to be complete six weeks after the drug was stopped.

Termination of therapy became necessary in a fourth patient during the 30th week of treatment with iproniazid because of the development of signs of an encephalitis. This case was believed to be of sufficient importance to report in detail elsewhere,[10] since at autopsy, one week later, multiple petechial hemorrhages, thought to be indicative of a toxic encephalitis, were present in the brain. It is recognized that proof of a causal relationship to the administration of iproniazid is lacking in this case as well as in those above, but one must recognize the highly suggestive clinical implications.

Causes of alteration of treatment in the combined-therapy group are also listed in Table 4. As can be seen, in six of those on iproniazid in combination with streptomycin or PAS, discontinuance was necessitated because of mental changes. These included a moderately severe depression in two; personality change characterized by uncooperativeness, aggressiveness, and hyperactivity in two; visual hallucinations in one, and loss of memory and inability to concentrate in one.

## COMMENT

The results obtained in the present series of patients confirm previous reports† that iproniazid is considerably more toxic than isoniazid and suggest, in addition, that side-effects are more frequent and more severe when it is given in combination with streptomycin or PAS. In spite of some apparent superiority over isoniazid in its benefits upon the symptoms of pulmonary tuberculosis, iproniazid appears too toxic for general use.

Isoniazid, on the other hand, in the dosage of 4 mg. per kilogram has proved to be relatively free from serious side-effects. It is worth recapitulating, however, the potentially serious reactions, which in our experience have appeared chiefly among those receiving iproniazid but all of which have also been observed by others in isolated instances among patients receiving isoniazid. These include mental changes, ranging from minor personality changes to frank psychoses; peripheral neuropathies; hemoptyses, and severe muscular spasms. In one instance in our series the latter reaction was thought to have been precipitated by the administration of meperidine hydrochloride during iproniazid therapy. Other reactions necessitating alteration of treatment among those receiving iproniazid have been postural hypotension, difficulty with micturition, increasing dyspnea, purpura, and hemoptysis. Mention should also be made of the possibility that a case of toxic encephalitis and one sudden death (ventricular fibrillation?) may have been related to therapy with iproniazid. Past experience has shown ‡ that increasing dosage has a direct relationship to frequency and severity of side-effects.

From a chemical standpoint, isonicotinic acid hydrazide compounds are related to nicotinic acid, a component of the vitamin B complex. Thus it is interesting that certain syndromes sometimes found in severe nicotinic acid deficiency have also been encountered during iproniazid and isoniazid therapy, examples of which are

† References 1, 3, and 8.

‡ References 8 and 9.

Korsakow's psychosis,[4] peripheral neuropathy,§ and, finally, frank pellagra.[7] While no conclusions may be drawn from these isolated reports, such observations should stimulate investigation of the possibility that isoniazid or iproniazid and nicotinic acid may act competitively in the body under certain circumstances.

The pharmacology of these compounds in the human body clearly involves the autonomic nervous system in some manner. Certain effects observed during administration of these drugs may be produced by direct stimulation of the sympathetic nervous system (constipation, dryness of the mouth) and of the parasympathetic system (difficulty with micturition, sweating, bradycardia, impotence, bronchospasm) as well as by blocking of the autonomic ganglia (postural hypotension). Administration of atropine to two of our patients, however, produced no significant amelioration of the bradycardia thought to be related to parasympathetic stimulation. In animals, autonomic effects could not be satisfactorily demonstrated in doses of 1 to 10 mg. per kilogram.[12] Thus, the mechanism of production of these effects in the human needs investigation.

The explanation for the unusual "withdrawal" syndrome is even more obscure. It is interesting that the symptoms observed upon termination of iproniazid are apparently peculiar to the drug, since they were not prevented by substitution of isoniazid, the parent compound.

## SUMMARY

Side-effects encountered among 42 patients receiving iproniazid and 35 patients given isoniazid show the former drug to be clearly the more toxic. Combinations of iproniazid with streptomycin or with *p*-aminosalicylic acid (PAS) appear more toxic than iproniazid used alone.

Termination or interruption of therapy, or reduction in dosage because of toxicity, was necessary for 45% of those receiving iproniazid and only 9% of those taking isoniazid.

While the majority of reactions to these compounds, particularly isoniazid, are minor, potentially serious effects include (*a*) mental changes, (*b*) peripheral neuropathy, (*c*) severe muscular spasms, and (*d*) hemoptysis.

Attention is directed to one case of encephalitis and one sudden death, possibly related to administration of iproniazid.

"Withdrawal" symptoms have been observed in 64% of 14 patients whose iproniazid therapy was abruptly terminated; these were not relieved by substitution of isoniazid.

Isoniazid has proved to be a safe drug for therapeutic use. Iproniazid is considered too toxic for general use.

§ Gammon, G.: Personal communication to the authors, and examples in the present series.

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# PERIPHERAL EMBOLISM BY METALLIC MERCURY DURING ARTERIAL BLOOD SAMPLING

## Report of Two Cases

WILLOUGHBY LATHEM, M.D.
WEST HAVEN, CONN.
GERSON T. LESSER, M.D.
WILLIAM J. MESSINGER, M.D.
AND
MORTON GALDSTON, M.D.
NEW YORK

ANAEROBIC * blood sampling from a peripheral vessel is a useful and often essential procedure in many diagnostic and experimental studies. Stadie [1] originally used mineral oil in the syringe to prevent contact between the blood and air. During the past 10 years the technique of sealing heparinized syringes with metallic mercury has been widely employed. The purpose of the present report is to point out an inherent danger in this technique which has apparently not been appreciated. In two different laboratories peripheral embolism has resulted from the accidental introduction of mercury into the arterial stream during blood sampling when syringes were prepared in the accepted manner.

### PREPARATION OF SYRINGES

Two or three drops of metallic mercury were added to 20 cc. heparinized Luer-Lok syringes. Excess mercury was expressed prior to sampling by inverting the syringe and slowly advancing the plunger as far as possible, so that only the nozzle and the small dead space between the distal end of the plunger and the barrel remained filled. This small amount of remaining mercury could not be ejected by additional pressure on the plunger. A thin film of mineral oil or stopcock grease served to maintain close contact between the sides of the plunger and the barrel. When thus prepared, the syringe was locked to the arterial needle and filled either by gentle suction or by pressure of the arterial stream.

CASE 1.—During a study of pulmonary function, on March 11, 1949, an indwelling 19-gauge Cournand needle was introduced into the right brachial artery of a 28-year-old healthy male physician. After minor manipulation a free flow of arterial blood was obtained, and one anaerobic sample was drawn for the determination of blood gases. After one hour, the needle was removed. At this time slight tingling was noted in the distal phalanx of the right fourth finger, and shortly thereafter a similar sensation occurred in the right fifth finger. One hour later, moderately

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Dr. Lathem's present address: Veterans Administration Hospital.

From the Department of Medicine, Columbia University College of Physicians and Surgeons, and the Presbyterian Hospital and the Research Service, New York University Division, Goldwater Memorial Hospital.

* The word "anaerobic" is strictly defined as pertaining to an organism "thriving best without air" (Gr. *a*, not; *aer*, air; *bios*, life). However, the word has been so frequently used in describing blood sampling to mean "without contact with air" that, for brevity, it is similarly used in this report.

severe throbbing pain developed in the distal phalanges of both fingers. Five hours after the arterial puncture, the pulp of these phalanges became swollen, red, and hot. A few small violaceous areas on the palmar surface and under the nails of the involved phalanges appeared several hours later and increased moderately in size by the next day. On the following day 200 mg. of benzazoline (Priscoline) was given. Pain in the involved fingers was intense and persistent initially but gradually subsided and disappeared by the fifth day. At this time the violaceous areas became nodular and small superficial abscesses appeared on the surface of many nodules. X-rays of the hand on this date showed an accumulation of opaque mercury globules in the soft tissues of the fourth and fifth distal phalanges (Fig. 1). Penicillin procaine injections and bishydroxycoumarin (Dicumarol) therapy were instituted at this time and continued for four days.

The swelling and redness remained unchanged during the first week and then began to subside gradually, disappearing entirely by the ninth day. Two days later, minute particles of mercury were noted in the skin of the finger tips, primarily in the necrotic areas over the nodules. The

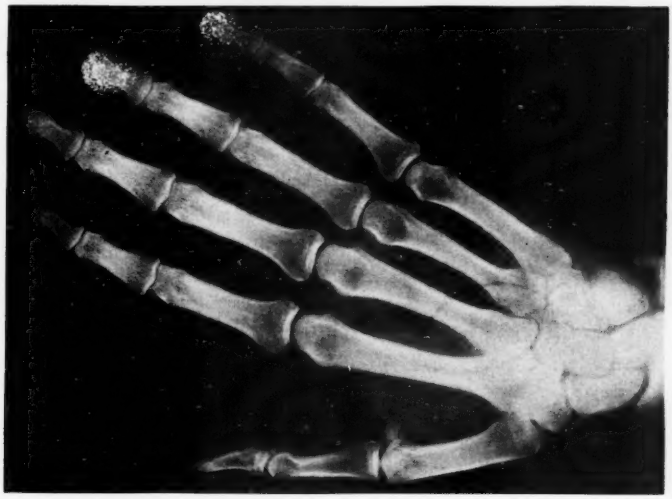

Fig. 1 (Case 1).—Mercury globules in fourth and fifth fingers five days after accident.

apices of the nodules gradually became black and necrotic. A smear of aspirated fluid from a nodule revealed innumerable polymorphonuclear leucocytes; culture proved sterile.

During the third week the superficial layers of skin of the terminal phalanges began to separate, and from April 8 to 14 superficial débridement was carried out every other day. Clean, pink, healthy tissue was present under the desquamated skin. From comparative x-rays of the involved fingers and exfoliated skin containing a small amount of mercury (7.5 mg. by weight) it was grossly estimated that roughly 1 gm. of mercury was present in the fingers one month following the accident. At this time new crops of tiny yellow nodules began to appear, and a small particle of mercury was noted in each nodule upon nicking the overlying skin. Essentially the same process—appearance of nodules, necrosis, sloughing of superficial skin with healthy tissue underneath—continued for about eight months, although the number of new nodules gradually decreased. From December, 1949, to the present (March, 1953) rare nodules have appeared, very few having been noted during the past year.

Although spontaneous pain disappeared entirely within four to five days of the accident, exquisite tenderness on slight trauma to the fourth and fifth finger tips persisted for about one year. In June, 1950 (15 months after the accident), clubbing was noted in both the affected fingers, and this has persisted. Aside from the clubbing and the appearance of an occasional small

nodule, the fingers have been completely asymptomatic for about three years. There has been no pain, no diminution of function or sensory perception, and no evidence of significant circulatory abnormality.

No symptoms other than those in the local area were observed at any time. During the first few weeks after the accident numerous red and white blood cell counts and urinalyses were within normal limits. Repeated analyses of the urine for mercury were negative.

Follow-up x-rays of the affected digits revealed gradual diminution in the number and size of the metallic particles over a period of months. The most recent film (November, 1952) showed a considerable decrease in the number and density of the mercury particles (Fig. 2).

CASE 2.—A 37-year-old housewife was admitted to Presbyterian Hospital on Aug. 8, 1952, with a diagnosis of Hodgkin's disease. Physical examination was negative except for slight enlargement of the left supraclavicular lymph nodes; blood pressure was 120/80, and there was no evidence of peripheral vascular disease. Routine laboratory studies were within normal limits except for an elevated sedimentation rate (84 mm. in one hour) and widening of the mediastinum by x-ray.

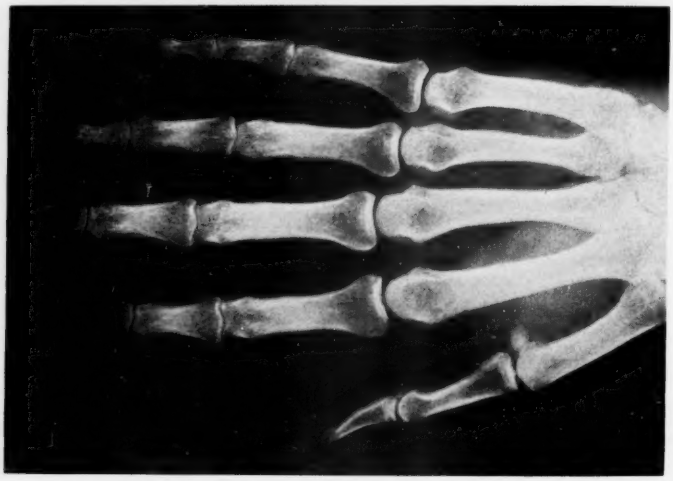

Fig. 2 (Case 1).—Almost complete disappearance of mercury three and one-half years after accident.

On Aug. 28, during measurements of renal function, six anaerobic blood samples were taken over a three-hour period through an indwelling 18-gauge Cournand needle lying in the right brachial artery. The arterial puncture was atraumatic, there was no evidence of clot formation within the needle, and all samples were freely withdrawn. L-arterenol (l-Nor-epinephrine) (1.34 mg. in 56 minutes), inulin, and sodium bicarbonate were administered by infusion through a vein in the right wrist. Blood pressure was maintained at 150 to 160/85 to 88 during infusion, and no untoward reactions occurred. During the last hour of the study the patient complained of discomfort in the right elbow and around the arterial puncture site and of pain and stiffness in the fingers of her right hand. No discoloration, pallor, or cyanosis were noted at this time. An hour after withdrawal of the arterial needle, pain in the right hand became intense, requiring codeine and meperidine (Demerol), and several hours later slight swelling of the third and fourth fingers was apparent. The following day definite nailbed cyanosis was noted in all fingers of this hand, most marked in the third and fourth digits, and pain was quite severe. On the second postpuncture day all fingers on the right were warmer than those on the left and swelling and clearly delineated reddish cyanosis were visible in the fingers anteriorly and in the palm just proximal to the metacarpophalangeal joints. Discoloration extended to the finger tips but included only the nailbeds and distal phalanges dorsally. Antispasmodic (benzazoline and dioxyline phos-

phate [Paveril]) and antithrombotic (heparin and bishydroxycoumarin) therapy were instituted. Two successful right stellate ganglion blocks afforded prompt, though incomplete, subjective relief, and definite improvement of color was noted in all fingers, with the exception of the terminal phalanges.

During the following three days pain continued unabated and little change was noted. Gradually rubor became the dominant color, cyanosis slowly receding. At the end of one week pain was less intense and plethysmography was possible in the right index finger. Pulse amplitude

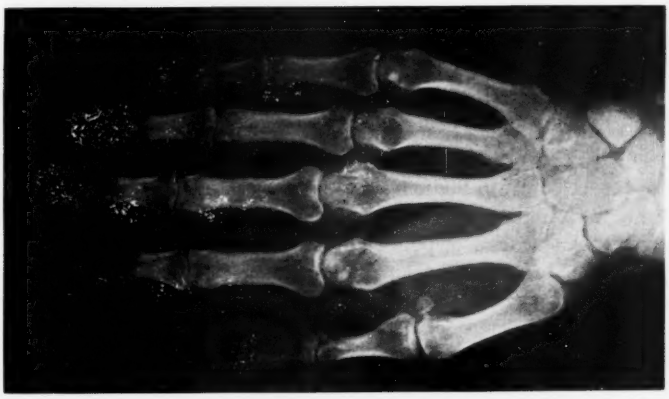

Fig. 3 (Case 2).—Mercury particles in fingers one and one-half months after arterial puncture.

Fig. 4 (Case 2).—Mercury in soft tissues around elbow and along forearm.

in this digit was three to four times greater than on the left. By the 11th day redness of the palm and proximal phalanges had begun to fade, although the third, fourth, and fifth fingers remained swollen and very tender. At this time several firm bluish-black nodules appeared in the tips of all fingers. These nodules resembled small abscesses undergoing early necrosis. Similar lesions were noted in several small circumscribed areas on the medial aspect of the right elbow.

The hand slowly improved. Although slight desquamation occurred about the finger tips with little change in the appearance of the nodules, the discoloration, pain, and tenderness gradually resolved until at time of discharge, on the 25th day, only slight swelling and erythema remained.

During the following month continued improvement in the hand was observed, although some stiffness of the elbow and fingers and tenderness over the nodules persisted.

An x-ray of the right hand (Fig. 3) on the 46th postpuncture day showed scattered metallic material in the soft tissues of the fingers, particularly in the distal phalanges of the third and fourth digits. Similar material was present in the soft tissues around the elbow and along the forearm (Fig. 4). Microscopic sections of skin disclosed a proliferative inflammatory reaction. There was dilatation of the blood vessels with mural thickening and some recanalization of the smaller and larger arterioles secondary to thrombosis. No measurements of urinary mercury excretion were made, but routine urinalyses were consistently negative.

## COMMENT

The injection of metallic mercury into the blood stream is a rare occurrence, and little is known of its local and systemic effects. Umber [2] describes a patient in whom 27 gm. (2 cc.) of metallic mercury were injected intravenously with suicidal intent. The metal lodged in the lungs and led to symptoms of mild mercury poisoning (diarrhea, abdominal pain, and gingivitis) followed by complete recovery. Four years later the patient died of pulmonary tuberculosis, and at autopsy globules of mercury were found in the heart, lung, kidneys, spleen, and large bowel. Other than a mild foreign-body reaction surrounding the globules, some of which were encapsulated, no pathological changes could be attributed to the mercury.

That mercury poisoning did not develop in the two cases reported here may be attributed to the small amount injected and to the slow ionization and highly nonreactive chemical nature of metallic mercury. Such factors appear to account for the absence of poisoning when roughly comparable amounts enter the subcutaneous tissue by absorption from skin ointments [3] or by direct penetration from broken thermometers.†

In Case 1 roughly 95% of the mercury originally present in the fingers disappeared over a four-year period (Fig. 2). While the greatest loss probably occurred by ejection through the skin, it is possible that trace amounts were slowly ionized and removed from the body via the kidneys and gastrointestinal tract in quantities too small to be detected by the methods used.

In both cases the initial symptoms apparently resulted from embolism of the glomera and capillaries in the fingers, with secondary spasm and thrombosis of the larger arterioles. Later, as spasm subsided, blood flow increased and a painful foreign-body reaction appeared, with the formation of sterile abscesses around tiny mercury particles, some of which were extruded from the abscesses or directly through the skin. Similar foreign-body reaction and abscess formation have been described following injury with a broken thermometer.[4]

The late development of clubbing in Case 1 (not enough time has elapsed to know whether this will also occur in Case 2) is of considerable interest, although its pathogenesis is unclear. Unilateral clubbing has been described in association with aneurysmal dilatation of the large arteries supplying the arm, in a brachial arteriovenous aneurysm, and, rarely, in Raynaud's disease and erythromelalgia,[6] but apparently not as a result of embolism or other diseases of the peripheral arteries. It is interesting that clubbing may occur in subacute bacterial endocarditis, a condition associated with multiple embolic phenomena in small peripheral blood vessels.

† References 4 and 5.

Mercury was deposited in all fingers in Case 2 but only in the fourth and fifth fingers in Case 1, possibly owing to a positional difference in the hands at the time of accident. In the latter, the ulnar portion of the forearm and hand were dependent, mercury apparently gravitating to the arteries supplying the fourth and fifth fingers. The exact position of the hand in Case 2 was not noted.

The manner in which mercury escaped from the syringe and entered the artery is obscure. It is possible that a small, undetected excess at the tip of the syringe entered the needle by gravity during attachment or that, during withdrawal of blood, the plunger was inadvertently advanced, expressing mercury which lay near the tip. In any event, there seems to be no valid reason for the use of mercury during anaerobic collection of blood. It is quite simple to fill the small airspace in the syringe with heparin or oxalate solution. If later mixing of blood is desired, the tip of the syringe may be inserted below the surface of a pool of mercury and a small amount withdrawn. This procedure is now routinely followed in our laboratories. It is recommended that a similar method be utilized in all anaerobic blood sampling to avoid repetition of these unfortunate accidents.

SUMMARY

Two cases are described in which multiple arterial embolization of the fingers resulted from accidental injection of metallic mercury into the brachial artery during anaerobic blood sampling.

No evidence of mercury poisoning appeared in either case. In both, symptoms of circulatory insufficiency of the fingers gradually disappeared, although foreign body abscess formation and elimination of the mercury through the skin continued for a prolonged period.

In one case clubbing of the involved fingers was noted 15 months after the accident and appears to be permanent.

It is recommended that the use of mercury be avoided in the preparation of anaerobic syringes.

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# TREATMENT OF BACTERIAL PNEUMONIA WITH ERYTHROMYCIN

WAYNE S. WADDINGTON, M.D.
FRANCIS M. MAPLE, M.D.
AND
WILLIAM M. M. KIRBY, M.D.
SEATTLE

ERYTHROMYCIN, a derivative of Streptomyces erythreus, is effective chiefly against Gram-positive bacteria, and in this respect it resembles penicillin.[1] Perhaps the most promising attribute of this antibiotic is its effectiveness against strains of staphylococci which are penicillin-resistant. Pneumococci and streptococci are also highly sensitive to erythromycin, and blood levels which are highly effective against these organisms are readily obtained following oral administration of the drug.[2] Side-reactions are rare and consist for the most part of mild gastrointestinal disturbances.

The present study was undertaken to evaluate erythromycin in the treatment of adult patients with pneumonia caused by Gram-positive bacteria.

## METHODS AND MATERIALS

Seventy-five adult patients admitted to the infectious disease ward of King County Hospital from July, 1952, to July, 1953, with bacterial pneumonia were treated with erythromycin. The patients were predominantly in the older age groups. Many were suffering from the multiple concomitant diseases which are so common among the indigent and the aged, and a large percentage were severe alcoholics. Sixty patients were men, and 15 were women. Only 14 were under the age of 40 years; 47 were 50 years or over, and 16 were over 70 years (Table 1).

At the time of admission the patients were all acutely ill and displayed x-ray and physical findings characteristic of an acute pneumonic process. Besides the routine examination of blood and urine, laboratory studies included a direct smear of the sputum, a sputum culture, and a blood culture. Pneumococci were isolated from the sputum of 43 of the 75 patients and from the blood stream of 11 patients. In the other 32 cases the sputum smears contained large numbers of Gram-positive cocci, but the sputum cultures showed no clear-cut predominating organism. In many instances, especially in the older and sicker patients, it was impossible to obtain an adequate specimen of sputum for culture. It is probable that the majority of these patients had pneumococcal pneumonias, since the clinical and x-ray findings and response to therapy were characteristic of pneumonia caused by this organism. Indeed, in 2 of the 11 patients with positive blood cultures pneumococci were not isolated from cultures of the sputum. Susceptibility of pneumococci to erythromycin was determined by the tube-dilution method in 29 cases. In all 29 growth was inhibited by 0.1 $\gamma$ per cubic centimeter. Previous studies in patients have demonstrated that blood levels greatly in excess of these values are easily attained by either the intravenous or the oral route.*

Thirty-five patients were considered seriously ill; 34, moderately ill, and, 6 mildly ill, as determined by clinical appearance, fever, and extent of x-ray and physical findings. Patients

From the Department of Medicine, University of Washington School of Medicine, and the King County Hospital.

* References 2 and 3.

were treated with erythromycin when Gram-positive cocci were found to be the predominating organism on direct smears of the sputum, without waiting for the results of blood and sputum cultures.

Patients were given either 0.3 or 0.5 gm. of erythromycin at 3:00 and 9:00 a. m. and at 3:00 and 9:00 p. m., so that food would not interfere with the absorption of the antibiotic. The drug was administered in acid-resistant tablets, which dissolve only in an alkaline medium, such as prevails in the small intestine.

TABLE 1.—*Status of Patients on Admission*

| | Patients, No. | | Patients, No. |
|---|---|---|---|
| Age, yr. | | Severity of illness | |
| 10-19 | 0 | Severe | 35 |
| 20-29 | 6 | Moderate | 34 |
| 30-39 | 8 | Mild | 6 |
| 40-49 | 14 | | |
| 50-59 | 16 | Day of illness on which therapy was started | |
| 60-69 | 15 | 1 | 6 |
| 70-79 | 12 | 2 | 7 |
| 80-89 | 3 | 3 | 7 |
| 90 and over | 1 | 4 | 10 |
| | | 5 | 5 |
| WBC on admission | | 6 | 3 |
| 4,900 and under | 0 | 7 and over | 31 |
| 5,000-10,000 | 15 | Uncertain | 6 |
| 10,000-15,000 | 14 | | |
| 15,000-20,000 | 19 | | |
| 20,000-30,000 | 18 | | |
| 30,000 and over | 9 | | |

TABLE 2.—*Results of Therapy*

| No. Days After Therapy Begun for Temperature to Reach and Remain Normal | Cases, No. |
|---|---|
| 1 | 21 |
| 2 | 22 |
| 3 | 12 |
| 4 | 5 |
| 5 or more due to urinary tract infection (one died) | 2 |
| 5 or more due to skin infection | 1 |
| 5 or more due to complications of pneumonia | |
| Delayed resolution | 6 |
| Pleural effusion (one died) | 4 |
| Superinfection with Gram-negative bacilli and subsequent development of pneumococcic meningitis | 1 |
| Moribund on admission and died | 1 |
| Total cases | 75 |

## RESULTS

On the basis of clinical appearance of the patient, subsidence of fever, decrease in sputum production, and clearing of physical and x-ray signs of pneumonia, the response to therapy was considered good in 63 of the 75 cases (84%). Twenty-one patients became afebrile (oral temperature 99 F. or less) within 24 hours after the initiation of erythromycin therapy and remained afebrile for the remainder of their hospital stay. Twenty-two patients required two days; 12 patients, three days, and 5 patients, four days to become consistently afebrile (Table 2). Thus, 60 of the 75 patients, or 80%, had normal temperatures within 96 hours after erythromycin therapy was begun.

Three patients who showed striking improvement in their pulmonary findings continued to have low-grade fever for over five days after therapy was begun. Two of these patients had urinary tract infections, and one had infected skin abrasions to account for the sustained temperature elevation. One of the patients with a urinary tract infection later died of unknown cause and will be described in another section.

The good response which occurred in 63 of the patients may be exemplified as follows: A patient would be admitted with a five- or a six-day history of fever, cough productive of yellow or rusty sputum, chest pain, anorexia, and weakness. Physical and x-ray examinations would reveal signs of consolidation over one or more lobes, and sputum smears would show large numbers of Gram-positive cocci. Within two or three days the patient would be afebrile, comfortable, taking food and fluids well and would be discharged on the seventh to ninth hospital day.

Complications occurred in 11 cases, as noted in Table 2. The four patients with sterile effusions showed sustained temperature elevation until the fluid was aspirated or spontaneously resorbed. One of these patients died later with heart failure and uremia, while the other three recovered. No patient developed empyema. In six cases fever persisted longer than five days after therapy was begun and there was slow clearing of physical and x-ray signs. In none of these was there evidence of bronchial obstruction, lung abscess, effusion, or infection outside the lung. These are considered to be instances of delayed resolution. It is interesting to note that four of these patients were middle-aged alcoholics, while the other two were over 75 years of age. These six patients all recovered. A superinfection with Gram-negative bacilli developed in one patient.

A 49-year-old white man was admitted severely ill with pneumonia of the right upper and lower lobes and a white cell count of 22,800, and pneumococci were cultured from the blood stream. On erythromycin therapy his temperature, which had been 103.2 F. on admission, fell to normal after two days. On the fifth hospital day his temperature rose again to 103.8 F., at which time a sputum smear showed large numbers of Gram-negative rods. Erythromycin was discontinued, and he was given chloramphenicol, 0.25 gm. every six hours. The temperature fell slowly to normal over a period of several days, and he appeared greatly improved. On the 14th hospital day, while still on chloramphenicol therapy, he developed pneumococcic meningitis, which was successfully treated with massive doses of penicillin.

The 11 patients with positive blood cultures merit special comment. Prompt and uneventful recovery occurred in six of these patients. Two had delayed resolution, with a prolonged febrile course, but recovered completely. One had a sterile effusion and recovered after repeated aspirations. As described in the preceding paragraph, one patient developed a superinfection with Gram-negative bacilli. The 11th patient had an overwhelming pneumococcic infection and will be described below. Three patients died.

The first was a 35-year-old white man who had lobar pneumonia complicated by alcoholism with delirium tremens. His leucocyte count was 600 per cubic millimeter, and pneumococci were cultured from the blood stream. The patient was moribund on admission and died eight hours later, despite therapy.

The second death occurred in an 83-year-old white woman who had right lower lobe pneumococcic pneumonia with sterile effusion, mild congestive heart failure, and uremia. After four days of erythromycin therapy the temperature fell to normal and she appeared considerably improved. The uremia did not respond to treatment, and she died on the 18th hospital day. Autopsy disclosed bilateral bronchopneumonia, a 1,000 cc. right hydrothorax, left ventricular hypertrophy, sclerosis of the coronary arteries, and advanced nephrosclerosis.

The third was a 74-year-old white man who died suddenly of unexplained cause on the 23rd hospital day. He had been successfully treated with erythromycin for right lower lobe pneumonia with satisfactory clearing of physical and x-ray signs. He was subsequently treated with oxytetracycline for a urinary tract infection. Convalescence was proceeding well at the time of his sudden and unexpected death. Permission for autopsy unfortunately was not obtained.

## COMMENT

The results of erythromycin therapy of bacterial pneumonia in the present study were in general good and appeared to be comparable to those obtained in similar series of patients treated with penicillin, chloramphenicol, oxytetracycline, and chlortetracycline.† Sixty (80%) of the 75 patients became afebrile (oral temperature 99 F. or less) within four days after therapy was begun and remained afebrile for the remainder of their hospital stay. These results are particularly significant since the majority of the patients were either severe alcoholics or were elderly and debilitated.

The favorable results observed in this study are not surprising in view of the high blood concentrations of erythromycin which are readily attained in patients and the marked sensitivity of Gram-positive bacteria to the antibiotic. In the 29 instances in the present series in which the sensitivity of the infecting pneumococcus was determined in vitro, growth was inhibited by 0.1 γ per milliliter or less in every instance. In previous studies in this laboratory, serum concentrations of erythromycin higher than 2 γ per milliliter were consistently obtained in patients receiving 0.5 gm. of erythromycin by mouth every six hours. Over half the patients had levels of 10 to 20 γ per milliliter, while in isolated cases levels of 30 and 50 γ per milliliter were observed.[2] An intravenous preparation of erythromycin has recently become available and is indicated for patients too ill to take oral medications or for patients in whom it is desirable to obtain high blood levels immediately.[3]

Superinfections due to antibiotic-resistant staphylococci have been encountered with increasing frequency in patients with pneumonia treated with oxytetracycline, chlortetracycline, and penicillin. This complication did not occur in the present series and should be uncommon during erythromycin therapy, since most staphylococci are, at present, sensitive to this antibiotic. As is the case with penicillin, however, one must be alert for the development of superinfections due to Gram-negative organisms, such as occurred in one of our patients.

Intolerance to orally-administered erythromycin was encountered in only one patient, who had nausea and vomiting a few minutes after each dose of the medication. This ceased promptly after the drug was stopped. There were no cases of diarrhea, proctitis, or pruritus ani.

Although erythromycin cannot be said to be superior to penicillin and other antibiotics from a therapeutic standpoint, it possesses certain features which make it a desirable agent for the treatment of bacterial pneumonias. Its chief advantages are that it is well absorbed when administered by the oral route, it causes few side-reactions, and superinfections due to staphylococci are unlikely to occur.

## SUMMARY AND CONCLUSIONS

Seventy-five adult patients with bacterial pneumonia were treated with erythromycin. Pneumococci were recovered from the sputum of 43 patients and from the blood stream of 11. Although many were alcoholics or debilitated and elderly, 63

† References 4-6.

patients responded promptly and made an uneventful recovery. One patient was moribund on admission and died within a few hours after therapy was begun. Eleven patients had complications of pneumonia, consisting of delayed resolution in five cases, sterile effusion in four, and a superinfection with Gram-negative bacilli in one. Two patients who initially showed improvement later died of other causes.

The results are considered to be comparable to those obtained with the broad-spectrum antibiotics and with penicillin. Side effects were negligible, consisting of nausea and vomiting in only one case. It is concluded that erythromycin is highly effective in the treatment of pneumonia due to Gram-positive bacteria.

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# PHENYLBUTAZONE (BUTAZOLIDIN), A USEFUL CHEMOTHERAPEUTIC AGENT FOR HODGKIN'S DISEASE

A. ROTTINO, M.D.
A. JOFFE, M.D.
AND
G. HOFFMANN, M.D.
NEW YORK

IT IS THE purpose of this paper to present an evaluation of the therapeutic efficacy of phenylbutazone * in Hodgkin's disease. The study covers a period of 18 months, during which time sufficient data were accumulated on 35 patients with Hodgkin's disease to make evident a pattern of therapeutic response and to delimit its usefulness insofar as this disease is concerned.

We shall not review the literature pertaining to the chemistry or pharmacology of phenylbutazone nor its effects on diseases other than Hodgkin's disease. This has been done adequately by others,† but up to now only one reference [3] has appeared in the literature as to its effect on Hodgkin's disease. This one report states briefly that after a single intramuscular injection of the drug into one patient with Hodgkin's disease there followed reduction of fever, subsidence of pain, and improvement of general condition and appetite.

## MATERIAL

In Table 1 are presented data describing the group we studied, giving sex, age, and the duration of established Hodgkin's disease. Most patients had already had many forms of therapy, but a few, who had been recently diagnosed, were as yet untreated. Symptomatology, nutritional state, extent of generalization of the disease, and size, number, and distribution of lymph node masses varied. Three patients were in a terminal state; others had become refractory to x-ray and methyl-*bis* ($\beta$-chloroethyl) amine hydrochloride (nitrogen mustard) therapy and were bordering on the preterminal phase.

In addition to clinical observations, the following laboratory studies were made: Red blood cell, white blood cell, platelet, and eosinophile counts; liver-function tests (Hanger and thymol turbidity tests and alkaline phosphatase, cholesterol, cholesterol ester, serum albumin, and serum globulin determinations), and electrophoretic study of blood serum.

Clinical observations were made concurrently by the three authors.

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From the Hodgkin's Disease Research Laboratory and the Department of Medicine, The St. Vincent's Hospital of the City of New York.

* Phenylbutazone (Butazolidin) was supplied by Geigy Pharmaceuticals, Division of Geigy Company, Inc., through the courtesy of Dr. A. Hemming, who in a personal communication suggested this study.

† References 1 and 2.

*Mode of Therapy.*—Except for one instance, the drug was administered by mouth in pill form, 200 mg. per pill, 1 pill two or three times a day with meals. Within a period varying from a few days to a week the dose was raised, in some instances, to 4, 5, and 6 pills daily and then maintained at these dosages up to four months continuously. As a rule, therapy was

TABLE 1.—*Pertinent Clinical Data for Thirty-Five Patients Receiving Phenylbutazone*

| Case, No. | Age, Yr. | Sex | Duration of Disease, Mo. | Previous Therapy * | | | Condition * |
|---|---|---|---|---|---|---|---|
| | | | | X-Ray | TEM | Nitrogen Mustard | |
| 1 | 48 | M | 7 | 0 | 0 | 0 | F |
| 2 | 59 | M | 6 | 0 | 0 | 0 | F |
| 3 | 28 | M | 14 | 0 | X | 0 | G |
| 4 | 27 | M | 60 | X | 0 | 0 | T |
| 5 | 32 | F | 11 | X | 0 | X | P |
| 6 | 28 | F | 78 | X | X | X | F |
| 7 | 33 | M | 15 | 0 | 0 | 0 | F |
| 8 | 24 | F | 30 | X | X | 0 | F |
| 9 | 32 | F | 42 | X | X | X | T |
| 10 | 29 | F | 53 | X | 0 | 0 | G |
| 11 | 32 | F | 34 | X | X | 0 | F |
| 12 | 47 | F | 7 | 0 | 0 | 0 | F |
| 13 | 36 | F | 18 | X | X | 0 | P |
| 14 | 57 | F | 36 | X | 0 | X | T |
| 15 | 37 | M | 48 | X | X | 0 | P |
| 16 | 21 | F | 23 | X | 0 | 0 | G |
| 17 | 17 | F | 54 | X | X | X | G |
| 18 | 21 | M | 82 | X | 0 | 0 | P |
| 19 | 16 | F | 29 | X | X | 0 | F |
| 20 | 26 | F | 126 | X | X | X | P |
| 21 | 23 | F | 9 | 0 | X | 0 | F |
| 22 | 67 | M | 18 | 0 | 0 | 0 | P |
| 23 | 23 | F | 78 | X | X | X | P |
| 24 | 24 | F | 73 | X | X | 0 | P |
| 25 | 55 | F | 66 | X | X | X | F |
| 26 | 36 | M | 112 | X | X | X | P |
| 27 | 29 | F | 10 | X | X | 0 | F |
| 28 | 38 | M | 114 | X | 0 | 0 | F |
| 29 | 32 | M | 12 | 0 | X | 0 | G |
| 30 | 47 | M | 42 | X | X | X | G |
| 31 | 21 | F | 14 | X | X | X | G |
| 32 | 28 | M | 18 | X | X | 0 | G |
| 33 | 57 | M | 42 | X | X | 0 | G |
| 34 | 20 | F | 96 | X | 0 | 0 | G |
| 35 | 26 | F | 96 | X | 0 | X | T |

* X, therapy given; 0, no therapy; F, fair; G, good; P, poor; T, terminal.

interrupted from time to time to resolve uncertainty as to the role it was playing in producing clinical and laboratory changes. Upon cessation of symptoms, medication was discontinued, and it was reinstated when they began again.

The total number of pills, the duration of the experiment, and the results are presented in Table 2.

RESULTS

The drug had a uniform action on pain and fever, as well as on the patient's general condition, and exercised a variable effect on pruritus and on lymph nodes. These effects will be discussed separately and illustrated with appropriate case reports.

TABLE 2.—*Period of Observation, Total Medication, and Symptomatic Response of Each of the Thirty-Five Patients* *

| Case, No. | Duration of Therapy, Mo. | Pills Taken, No.† | Control of Fever | Relief of Pain | Increased Strength, Well-Being; Less Fatigue | Pruritis Improved | Appetite Improved |
|---|---|---|---|---|---|---|---|
| 1 | 4 | 462 | — | — | X | X | — |
| 2 | 7 | 405 | X | X | X | X | — |
| 3 | ½ | 63 | — | — | — | — | — |
| 4 | ¾ | 63 | — | — | — | — | — |
| 5 | 2 | 280 | X | X | X | — | — |
| 6 | 4½ | 383 | — | — | X | 0 | — |
| 7 | ½ | 107 | — | — | X | — | X |
| 8 | 11 | 639 | — | X | X | X | X |
| 9 | 1 | 60 | — | — | 0 | — | — |
| 10 | 2 | 180 | X | X | X | — | X |
| 11 | 9 | 272 | — | X | X | — | — |
| 12 | 2½ | 715 | — | — | — | — | — |
| 13 | 11 | 620 | — | — | X | — | — |
| 14 | 2 | 2 | — | X | 0 | — | 0 |
| 15 | 2 | 417 | X | X | X | — | — |
| 16 | 7 | 430 | — | — | X | — | — |
| 17 | 8 | 500 | — | X | X | — | — |
| 18 | 7 | 200 | — | X | X | — | — |
| 19 | 11 | 271 | — | X | X | — | — |
| 20 | 11 | 610 | X | — | 0 | — | — |
| 21 | 11 | 656 | X | — | X | X | — |
| 22 | 5 | 168 | — | — | X | — | X |
| 23 | 11 | 742 | — | — | X | — | X |
| 24 | 11 | 614 | X | X | X | — | X |
| 25 | 11 | 791 | — | — | X | X | X |
| 26 | 7 | 546 | — | X | X | — | X |
| 27 | 1 | 111 | — | X | X | 0 | X |
| 28 | ½ | 42 | — | X | X | 0 | X |
| 29 | 1 | 81 | — | X | — | — | — |
| 30 | ½ | 12 | — | X | — | — | — |
| 31‡ | ¾ | 63 | — | — | — | — | — |
| 32 | 2 | 207 | — | — | X | — | — |
| 33 | 4 | 375 | — | X | — | — | — |
| 34‡ | 2 | 82 | — | — | — | — | — |
| 35 | ½ | 36 | — | 0 | — | — | — |

* —, patient did not have this symptom; X, patient relieved of this symptom; 0, patient not relieved of this symptom.

† Each pill contained 200 mg. of phenylbutazone.

‡ No effect on lymph nodes.

*Pain.*—The most striking effect was on pain. Eighteen of 35 patients exhibited this symptom. It was of the deep-seated type characteristic of this disease, located in the chest, back, upper abdomen, and lower extremities. The pains were usually

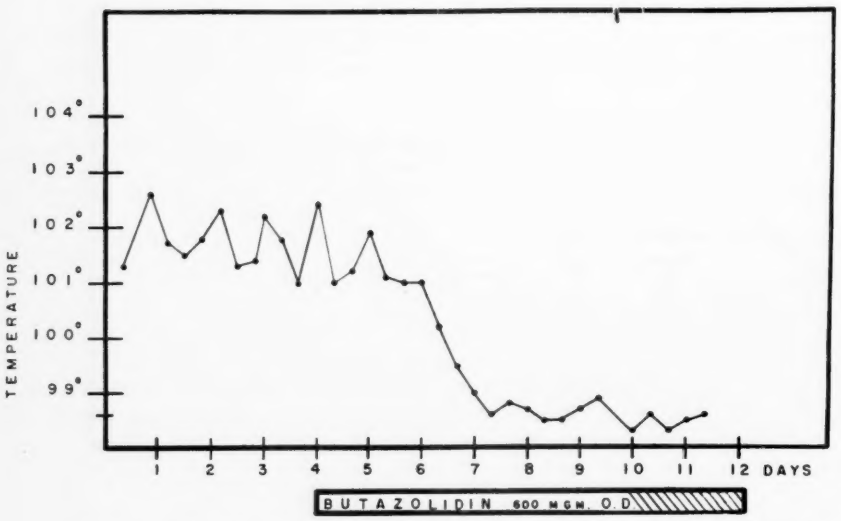


Fig. 1 (Case 1).—Fever of one week's duration. Temperature dropped to normal on the third day of phenylbutazone administration.

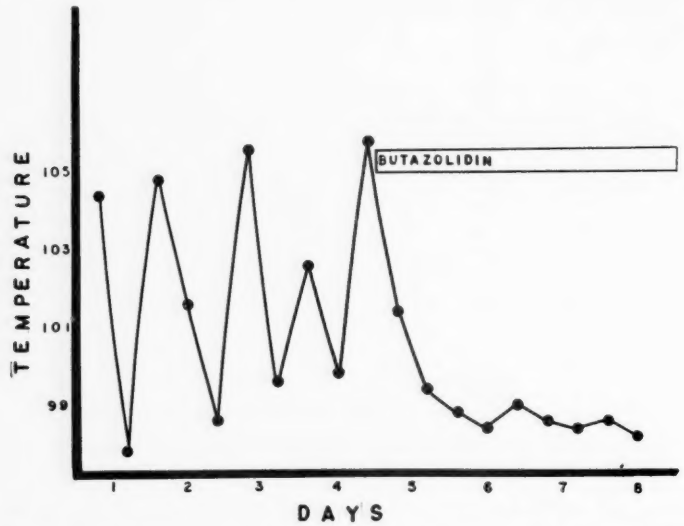


Fig. 2 (Case 27).—Septic type of temperature. See report of this case (Patient E. F.) in text. Temperature became normal 24 hours after phenylbutazone therapy was started.

constant, gnawing, worse at night, and, in some instances, severe. Also, in some instances they were associated with demonstrable node enlargement and bone involvement, but this association was not always demonstrable.

The results following phenylbutazone therapy were gratifying in all but one patient, who was a drug addict and in the terminal phases of the disease. Relief occurred as a rule promptly, either after 2 or 3 pills or after an interval of two to three days. In one instance there was no relief for one week on 3 pills a day,

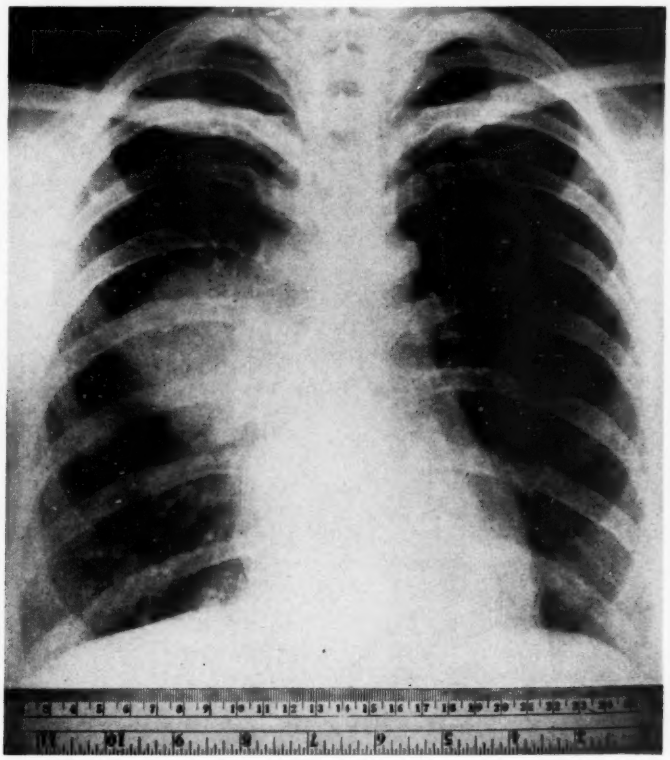

Fig. 3 (Case 21).—X-ray taken May 23, 1952, showing a large perihilar infiltrate. Phenylbutazone therapy was started at this time.

but when the dose was increased to 6 pills the pains disappeared. In three patients the pain recurred two months after cessation of medication. In each instance relief of pain followed readministration of the drug. One patient responded six times in a period of 17 months.

*Pruritus.*—The response of this symptom to phenylbutazone was variable, inconstant, and temporary. In several instances the cessation of pruritus was definite and striking but, unfortunately, the symptom recurred three to four months later and was from that time on no longer controllable with the drug. In one of these patients the pruritus subsided subsequently upon administration of triethylene melamine, whereas previously her condition had been refractory to it.

*Appetite.*—In 10 instances phenylbutazone induced ravenous appetites, which lasted two or three weeks and then tapered to normal. Others, terminal patients in whom anorexia was a serious problem, derived no benefit in this respect.

*Gain in Weight, Well-Being, Loss of Fatigue, and Strength.*—Several patients gained weight up to 15 lb. (6.75 kg.) as a result of improved nutrition. Since phenylbutazone frequently causes edema, it is necessary to distinguish between nutritional improvement and weight gain due to water retention. Gain in strength and well-being and loss of fatigue proved striking in many instances.

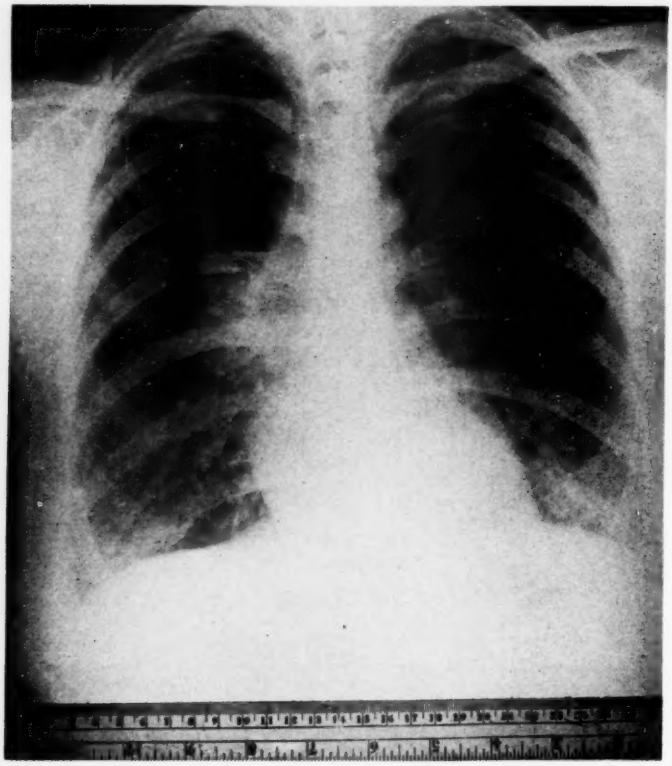

Fig. 4 (Case 21).—X-ray taken Feb. 11, 1953, after nine months of phenylbutazone therapy. A diminution in the size and density of the perihilar infiltrate has taken place.

*Fever.*—Control of fever is striking. Persistent temperatures of 104 F. drop by lysis or crisis and remain down even after the drug is withheld for periods as long as three weeks. There is concurrent control of sweats and chills, as well as return of normal body temperature (Figs. 1 and 2).

*Lymph Nodes.*—Results have been inconstant and variable but are not without interest. In a few patients there was a short temporary regression of nodes, followed by prompt return when the administration of the drug was stopped. Sometimes nodes began to increase in size during administration of the drug. In some

patients nodes not previously detected appeared and have grown steadily. Very curiously, a mass present in the axilla of one patient for three years disappeared in one week during therapy with phenylbutazone, but new nodes in the vicinity appeared simultaneously. In a second patient a parenchymal lung infiltrate present several months disappeared completely and, at the same time, nodes appeared in the groin. In still another instance a large parenchymal infiltrate radiating out from the right hilum, present at least seven months, diminished in size during phenylbutazone therapy (Figs. 3 and 4). Six months later, despite continuation of this form of treatment, the mass increased to its original size.

*Toxic Symptoms.*—Varying degees of edema developed. A few patients gained up to 20 lb. (9 kg.) from this cause, but discontinuance of the drug for one week led to diuresis and adjustment of water balance. In other instances, adjustment occurred spontaneously while the drug was still being taken. The marked edema of one patient, which developed during the first course of phenylbutazone, disappeared upon interruption of medication, and he was then able to tolerate a smaller dose sufficient to control temperature. This was the only instance in which edema was sufficient to cause concern.

Since leucopenia, anemia, and thrombocytopenia occur as a normal complication of Hodgkin's disease, the reported [4] toxic effect of phenylbutazone upon the hemopoietic system was the source of much concern. However, in only one instance did the red cell count drop sufficiently to be alarming. The patient had Hodgkin's disease in the advanced stage; hence, the anemia could have occurred regardless of medication. We noted no definite improvement in the hematologic status of the patients already anemic, leucopenic, or thrombocytopenic.

*Liver-Function Tests.*—Previous study ‡ had shown us that Hodgkin's disease frequently affects the liver, as indicated by abnormal values obtained in liver-function tests such as the Hanger and the thymol-turbidity tests. We could observe no evidence of enhanced liver damage resulting from administration of phenylbutazone; on the contrary, there were several instances of reversal of tests to normal. We do not, however, accept this as indicating favorable action by phenylbutazone but rather as evidence that in our patients there was no harmful effect on the liver.

*Skin Reaction.*—Skin rash occurred in only one case. This was mild and not bothersome. It disappeared when the drug was withheld and failed to recur when the administration was reinstituted.

## REPORT OF CASES

CASE 25.—*Pruritus*

J. L., a 51-year-old white woman, had known Hodgkin's disease of five years' duration. Throughout this period the patient had episodes of weakness and anemia. The main problem, however, was a most distressing pruritus, controlled at various times with x-ray therapy to a mediastinal mass, nitrogen mustard, triethylene melamine (TEM), and adenosin-5-monophosphate. In June, 1951, an episode of pruritus began that persisted and became increasingly more severe despite readministration of all the above drugs and x-rays. Phenylbutazone was first given March 21, 1952. A week later the pruritus subsided. Medication was discontinued on April 4, 1952, and five weeks later pruritus returned. The drug was given again for two

‡ Unpublished data.

weeks and again gave relief. Three weeks subsequent to discontinuance of a two-weeks' maintenance dosage, pruritus returned for the third time and, for the third time, responded to phenylbutazone therapy. This remission lasted for two months, but the next relapse proved refractory to treatment and became progressively more severe. During the next three and one-half months we tried phenylbutazone in combination with adenosin-5-monophosphate, with adenosine triphosphate, with procaine adenylate—all to no effect. Despite the fact that she had not responded to a course of TEM a year previously, the patient now got relief when this was tried again. Her pruritus diminished gradually and finally ceased entirely, and she has remained symptom-free to date.

CASE 23.—*Loss of Fatigue; Gain in Weight and Strength*

M. R., a 23-year-old white woman, had Hodgkin's disease of six years' duration. She had received at various times x-ray, nitrogen mustard, and TEM. At the time phenylbutazone was started, on March 12, 1952, there were pain, fever, sweating, and marked weakness of four days' duration. On 3 pills a day, symptoms were controlled within a week. After 28 days the drug was discontinued, owing to the fact that a persistent edema had developed. A month later, after the edema subsided, the drug was started again to see whether it would affect a chain of small nodes which, in the interim, had appeared in the neck. She was maintained on 3 pills daily for four months. During this period she had remarkable energy and felt unusually well, but there was no effect on the nodes. Edema, which reappeared, subsided spontaneously. Use of the drug was discontinued Nov. 14, 1952. Two weeks later the patient was so weak she could scarcely drag herself to the clinic, and hospitalization was contemplated. Instead, she was again given phenylbutazone, 3 pills daily. Strength and well-being returned promptly and were maintained despite the development of edema. Use of the drug was continued for two months and then stopped in February. In three days an alarming weakness developed. Phenylbutazone was started once more, and in four days there was the same remarkable pick-up, which lasted until July 6, despite the development of edema, when again the drug was discontinued. In one week the asthenia returned and, in addition, fever became evident, the temperature reaching levels of 103 F. Medication was withheld until July 27, when for the fifth time Phenylbutazone was administered. In two days there was return of energy, loss of malaise and fever, and return of appetite. At present the patient is being maintained on 400 mg. daily and has no complaints.

CASE 27.—*Pain, Fever*

E. F., a 29-year-old woman, developed cervical and axillary lymphadenopathy in May, 1951, during the course of a pregnancy. The diagnosis of Hodgkin's disease was established by biopsy, and she received x-ray therapy to her neck, chest, and axilla after delivery of a normal child.

She was seen for the first time in this clinic in February, 1953, when she was referred for intractable low-back pain and generalized pruritus. She was given 6 tablets of phenylbutazone daily, and within one week the pain had almost completely disappeared and she developed a ravenous appetite. The pruritus, however, was not affected. After four weeks the dose was reduced to 3 tablets daily and she continued without pain. The pruritus was severe during this time. On July 3 therapy with phenylbutazone was discontinued, and 10 days later the patient was admitted to the hospital because of weakness, excruciating pain, and fever. Phenylbutazone was administered once more, 6 tablets daily. The temperature dropped by crisis (Fig. 2), and pain was immediately relieved, but the pruritus was not relieved.

## COMMENT

Phenylbutazone has been of practical value in our clinic in the therapy of Hodgkin's disease. Of great use is the ability with its administration to control pain, a symptom common in this malady, disturbing and not always controllable with x-rays and the mustard compounds. Since the danger of causing narcotic addiction in patients with Hodgkin's disease is real, one hopes that a wider experience with phenylbutazone will prove it an adequate substitute for narcotics in the control of this symptom.

Patients with advanced and terminal Hodgkin's disease may have long periods of low-grade fever—temperatures of 99, 100, and 101 F.—or persistent fever at high levels—temperatures of 104 and 105 F. The control of temperature with phenylbutazone in these patients is definitely worth achieving, particularly when therapy with x-rays or nitrogen mustard is not feasible or is useless. An advantage possessed by phenylbutazone is that it lowers the temperature and is not usually associated with drenching sweats, and, further, the temperature may remain normal for weeks after the drug is stopped.

Further value of the drug arises from the fact that a certain number of patients improve nutritionally, showing an increase in weight. Others enjoy improvement of appetite, a feeling of well-being, loss of fatigue, and gain in strength. Although not all patients respond thus, the proportion who do is sufficient to make the use of the drug worth while.

The observed changes upon lymph node masses are inconstant and not sustained. For reducing these masses, it is by no means comparable to x-ray, nitrogen mustard, or triethylene melamine. Nevertheless, the fact that it does in some instances induce shrinkage is of interest in that it may have biological or biochemical significance. Microscopic examination of lymph nodes from three of our patients who experienced gross change in nodes showed, however, no histologic alteration of the usual Hodgkin's disease pattern. No specific change is observable in the lymphocytes, reticulum cells, or Sternberg-Reed cells, and one can only speculate as to what really happens. It is possible that the action is antiphlogistic and that the preliminary reduction of edema about and within the node permits operation of whatever mechanism it is which occasionally produces spontaneous subsidence of nodes.

No agranulocytosis or demonstrable liver damage resulted from medication. Since none of the patients who already had anemia, leucopenia, or thrombocytopenia, even those in whom these symptoms were severe, were made worse and since some actually improved, it seems reasonable to conclude that phenylbutazone is not specifically toxic to the bone marrow. The cases of agranulocytosis reported in the literature may possibly be ascribed to factors inherent in the individual patient which render the drug unsuitable for him.

The improvement we noted in patients with Hodgkin's disease in our opinion represents the action on symptoms and not specifically on the disease itself; this progresses despite medication. Nevertheless, the induced subsidence of pain, pruritus, fever, and sweating, and the improvement in nutrition make it possible for the patient to mobilize his own body defenses sufficiently to permit a spontaneous partial remission.

SUMMARY

The results of phenylbutazone therapy upon 35 patients with Hodgkin's disease have been studied over a period of one and one-half years.

The drug has been effective in the control of pain and fever, in the improvement of appetite, and in the promotion of well-being and lessening of fatigue. It has produced temporary relief of pruritus in some patients.

Several patients have manifested temporary regression of enlarged lymph nodes under therapy.

ADDENDUM

Since this paper was submitted the following article has appeared: Heilmeyer, L.; Harwerth, H. G.; Doxie, J., and Krauss, R.: Clinical and Experimental Investigations on the Effect of Butazolidin and Its Use in Leukemia, Neoplastic Processes and Lymphogranulomatosis, *Arzneimittel Forsch.* **3**:161, 1953.

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# SYPHILIS

## Review of the Recent Literature

HERMAN BEERMAN, M.D.

IRA L. SCHAMBERG, M.D.

LESLIE NICHOLAS, M.D.

PHILADELPHIA

AND

LAWRENCE KATZENSTEIN, M.D.

WILMINGTON, DEL.

With the Collaboration of Frank W. Reynolds, M.D., and T. Guthe, M.D., Geneva, Switzerland

THE CONTENT of this, the 18th annual review of syphilis, covering the period July 1, 1952, to July 1, 1953, continues to reflect the chief interest of the previous period.[1] There do not appear to be any outstanding discoveries, but the published and unpublished work on the phenomenon of treponemal agglutination in the serodiagnosis of syphilis offers tantalizing conjecture of what the future holds in the field of specific serodiagnosis of syphilis. General problems of serodiagnosis continue to receive adequate attention, but the large number of publications on the treponemal immobilization test (TPI test) indicates how the potentialities of this procedure have captured the imagination of workers from various countries. If this test only helps to clarify the problem of false positive reactions, as Moore and his co-workers maintain, the tremendous effort expended in its evaluation will be fully justified. Penicillin treatment of cardiovascular syphilis is now literally on a sound footing, since it has been demonstrated that ambulatory therapy of this phase of the disease is safe. The world problem of the treponematoses is rapidly coming under control through techniques of case finding (epidemiologic and serologic) as well as relatively economic and easily applied methods of mass therapy, admirably suited to the conditions existing in the endemic areas. At this point it is pertinent to acknowledge the inspiration afforded to the various people of the areas affected by the treponematoses by the workers of all parts of the world who, through their own efforts or under the aegis of the World Health Organization, have dedicated themselves to eradicate these diseases. Rosahn's study of the adverse influence of syphilis on longevity is perhaps the most inspired work in this period. In spite of the progress, several distressing developments have arisen. These are the increasing number of serious or even fatal reactions to the antibiotics and the growing realization that the problem of the venereal diseases (syphilis) is being changed in char-

Dr. Reynolds and Dr. Guthe are with the World Health Organization.

From the University of Pennsylvania, Departments of Dermatology, School of Medicine, Donald M. Pillsbury, M.D., Professor; Graduate School of Medicine, Herman Beerman, M.D., Chairman, and the Institute for the Study of Venereal Disease, Norman R. Ingraham, M.D., Director.

acter. This latter phenomenon is creating new tasks for the practitioner. For example, editorial comment in the *British Journal of Venereal Diseases* [2] points out that at the present time the belief continues to sweep the community that venereal diseases no longer constitute a danger to society or a challenge to medicine. This is due to publicity, to a steady decline in the early manifestations of the once fulminating disease, syphilis, and to the effects of therapy with the arsenicals and penicillin, which, in turn, have done much to modify the disease and to set up further waves of optimism. However, the shortcomings of therapy have developed a reservoir of late infection. Penicillin is creating an early stage of latency in syphilis. But despite today's optimism the physician interested in venereal disease has a responsible and busy future. His propaganda must teach the medical profession to appreciate the agent-host-treatment relationship, to realize the dangers of early latency from insufficient treatment, and to recall venereal diseases to their consideration in the differential diagnosis in all conditions. He must continue to remind obstetricians and other physicians of the need for continued watchfulness against congenital syphilis. When the opportunity arises, he must advise the public of the dangers of promiscuity and of the disasters arising from concealment of the disease and default from treatment and surveillance. He is not merely an epidemiologist, preventing the spread of venereal diseases in their early stages, but a physician whose skill will be taxed to combat late manifestations. T. J. Bauer [3] states that, while the venereal disease hunt is still on and substantial gains in reducing the incidence rates of syphilis are being made, the incidence of gonorrhea is declining at a much slower rate than that of infectious syphilis. Complete and accurate interviewing, professional education and training, effective public education, and improved diagnostic techniques and treatment, based upon research and evaluation, are necessary to assure a decline in incidence of gonorrhea comparable to that of syphilis. Likewise, Thomas [4] has discussed this problem. Like most relatively sudden and dramatic changes, the unprecedented decline in the reported cases of syphilis in the last five years has caused undue optimism in some quarters and unjustified skepticism in others. The truth should lie somewhere between these two extremes. It would be unrealistic to predict the swift eradication of a disease so complex in its clinical and epidemiologic aspects as syphilis. Yet the statement, "The long-term trends in the incidence of syphilis have not been altered by antibiotic therapy," would be almost equally unrealistic. Over 200,000 previously unreported cases of syphilis were reported in this country in 1951. During the same period, 3,500 cases were found in upstate New York. The fact that only 10% of newly reported cases were in the primary or secondary stages is an indication of difficulty in controlling this disease. There was an 80% decline in the number of cases of infectious syphilis in upstate New York in 1951 compared with the annual average of the five years preceding World War II. It is also the belief among physicians dealing with syphilis that there is less symptomatic syphilis than at any other time in the history of the nation. The anticipated postwar decline in syphilis rates and the decline in the virulence of the organism during the last century cannot explain the gains of the last five years. The antibiotics must have played an important role. Penicillin is greatly superior to any previously known antisyphilitic agent. The disadvantages of the arsenicals are discussed. Credit is given to the public health departments, without whose efforts neither penicillin nor any other antisyphilitic agent could have achieved the present gains in syphilis

control. The contributions of the New York State Department of Health Laboratory emphasized (1) the introduction of quantitative serologic tests for syphilis, (2) the discovery and the introduction of cardiolipin antigen, and (3) the Lange colloidal gold test. Many of the syphilis clinics in upstate New York have been closed, and the treatment of syphilis has been turned over to the private physician. The law of diminishing returns is coming into play. There is a temptation to do less with the few cases of syphilis which are discovered. It is thought by some persons that within the next decade late symptomatic syphilis will be as rare as typhoid fever. Thomas is essentially of the same opinion. The essentials of syphilis control, in summary, are (1) case finding, with particular emphasis on the poorer sections, where syphilis occurs more frequently; (2) interviewing patients with early syphilis for contacts at once and beginning treatment as soon as the diagnosis can be made; (3) prompt and thorough investigation of contacts; (4) serologic follow-up of treated cases of early syphilis at two- to three-month intervals for one to two years; (5) giving previously untreated or inadequately treated persons with persistently positive serologic tests for syphilis (STS) 6,000,000 units of penicillin even though the diagnosis may be in doubt (for cardiovascular or neurosyphilis 9,000,000 units of penicillin is the preferable total dose), and (6) treating acute gonorrhea with at least 600,000 units of penicillin procaine in oil and aluminum monostearate with a view to aborting simultaneously acquired syphilis.

Among the recently published sources of information are the general review of outstanding recent developments in the study of venereal diseases by Mikhail [5] and that of Wortmann.[6] The latter report covers precisely the same period as our 16th review (July, 1951, to July, 1952). The recent report of the World Health Organization [7] is a storehouse of information on most of the problems dealing with the treponematoses. The World Health Monograph Series,[8] dealing with the First International Symposium on Yaws Control, held in Bangkok, in 1952, also details much of the information in the present review. Florey's volume [9] represents the third of a proposed four-volume work concerned with the study of antibiotics, a subject termed by the publishers as a "new science." The parent monograph, a two-volume set entitled "Antibiotics," appeared in 1949 and dealt primarily with the chemical and pharmacological aspects of the then known antibiotics. The present book and an as yet unpublished fourth volume are intended to consider the clinical aspects, respectively, of penicillin and of other antibiotics. Chapter 5, pages 137 to 186, deals specifically with syphilis. Bruetsch's [10] data on syphilitic optic atrophy at last permits the optimistic statement that "the time has arrived when blindness due to syphilitic optic atrophy can be prevented. This achievement has been accomplished by the recognition of the early stages of the disease and particularly by the advent of successful treatment methods." In this book the subject is covered from every angle: historical background, incidence of syphilitic optic atrophy, its frequency in various types of neurosyphilis, and its relative incidence among optic atrophies of other causation. Grin's report [11] represents a monographic presentation of material previously published in the *Bulletin of the World Health Organization* (**7:** 1-74; 75-81, 1952) on the natural history and control of endemic syphilis, a treponemal disease of childhood. Hackett's [12] well-illustrated comparative study of the bone lesions of yaws and of syphilis should be valuable to the armed services and to medical missionaries.

### HISTORY OF SYPHILIS

Certain special aspects of the history of syphilis have been presented during this review period. Ibanez [13] has traced the story of syphilis from the days of Columbus to the times of Ehrlich. In another of his inimitable studies, Clarke [14] has evaluated Columbus, Charles VIII, and the serpentine disease. He offers what he considers a more plausible explanation for the initial appearance of syphilis in Europe than the Columbian theory.

Pazzini [15] reevaluates the ancient problem of syphilis and genius. The possibility cannot be excluded that syphilitic infection with its toxins and the changes it produces in the biochemistry of the brain cells may, within certain limits and in certain particularly gifted persons, constitute a stimulus to mental activity and creative capacity.

### TREPONEMA PALLIDUM AND OTHER TREPONEMES

The demonstration of spirochetes by various techniques and their cultivation and interrelationships have afforded material for a number of reports.

*Staining Spirochetes.*—E. T. Emura,[16] of the University of Cincinnati, reports a simple technique for staining spirochetes, using Parker 51 Superchrome blue-black ink concurrently with dark-field examination, in 50 cases of infectious syphilis, with good correlation.

The method is as follows: 1. A drop of serum and a small drop of Parker 51 blue-black ink are placed on one end of a clean glass slide. 2. Smearing is done rapidly, as in making a blood smear. 3. The smear is allowed to dry. This takes about two minutes. 4. Examination is done, using high dry or oil-immersion lens.

The spirochetes stain blue-black against a light blue granular background. Specimens may be kept without change in color for more than 12 months.

Vago [17] reports improvement in his staining technique for spirochetes. The new procedure comprises mordanting with tannin; boiling with dibromoxymercurifluorescine, and boiling with methylrosaniline chloride (Pyoktanin).

*Dark-Ground Illumination of Unstained Smears and Tissue Sections for Diagnosis of T. Pallidum.*—Coutts and his co-workers [18] are convinced that the epidemiological and economic advantages of dark-ground illumination of fixed unstained smears or tissue sections of suspected syphilitic material are numerous. They feel that the morphology and life cycle of treponemata can also be studied to advantage by the following simple technique: A thin smear of material is spread on a glass slide, fixed in 10% formalin solution for two minutes, washed in distilled water, and dried by blotting on filter paper. Room temperature is sufficient for drying and fixing the smear if it is to be examined within 48 hours. Tissue should be fixed in 10% formalin, imbedded in paraffin, cut in very thin sections, spread on a glass slide, and prepared as for staining, but not mounted. Smears and sections can be observed under simple immersion—oil only on the paraboloid condenser—or under double immersion. With the latter method, a cover glass is laid over the smear or section and a drop of cedar-wood oil is placed on its upper surface. After observation, the cover glass can be removed without damaging the preparation, which can be kept and observed as often as desired.

The structure of spirochetes has been the subject of various highly speculative descriptions, the most extreme being those in which certain authors claimed to be able to see an internal structure similar to that of trypanosomes in organisms only

0.3 $\mu$ in diameter. The use of the electron microscope, supplemented by the ultraviolet and phase-contrast methods, has now enabled a more exact study to be made, with the interesting result that all spirochetes are found to possess a common structural feature, which has not been found in any other type of organism. Bradfield and Cater [20] examined various species of Leptospira and Treponema, including Treponema recurrentis and T. pallidum, and also Cristispira balbianii, from the intestine of the oyster. In every species the spirochete was found spirally round the body from one end to the other, appearing sometimes inside and in other cases outside the cell membrane, the whole structure being "reminiscent of a piece of two-strand electric-light flex, in which strand *A* has become fatter (representing the main core of protoplasm) and strand *B* has become thinner and subdivided (representing the bundle of fibrils)." The use of mild tryptic digestion helped to reveal the details of this structure, the fibrils being much more resistant to trypsin than the other components of the protoplasm. The various species of Leptospira had only one fibril wound round the main core of protoplasm. Borrelia (Treponema) duttoni contained a bundle of about 8 fibrils and T. recurrentis a bundle of 15 to 20 fibrils within a cell membrane. The remarkable Cr. balbianii contained a very large number of fibrils closely wrapped in a spirally-wound bundle. After death the fibrils splayed out and produced an appearance similar to that of the undulating membrane of trypanosomes. It is interesting that no trace of this fibrillar structure has been found in the spirilla, a group of bacteria often considered to be closely related to spirochetes. The authors describe a simple model whereby it may be demonstrated that the form and behavior or spirochetes are consistent with the organization revealed if it be assumed that the fibrils are contractile and the protoplasmic coil elastic to some degree. Indirect evidence suggesting that the fibrils are in fact contractile is provided by the fact that during tryptic digestion they undergo changes similar to those seen in striated muscle fibers. The results of this study support the view that spirochetes constitute a highly specialized group, differing not only in their general physiology and pathology but also in their structural characteristics from other micro-organisms.

*Life Cycle of Treponemes.*—Treponemal buds, granules, and cysts were observed by Coutts and Coutts [19] in the study of human chancre serum examined in fixed but unstained smears under the dark-field microscope. Buds were usually found in intimate connection with or attached to the treponemal body. Numerous brilliant spherical bodies lying free in the serum and of variable density, as well as transparent spherules surrounded by a membrane containing a comma-like body in the interior, were observed. Larger rounded bodies which are considered to be multispirochetal cysts were also seen. All these structures were also seen in aspirated lymph from enlarged satellite lymph nodes. The authors consider these bodies to represent various stages of a complex life cycle of T. pallidum.

*Cultivation of Treponemes.*—In a paper well-supplied with the experiences of others, Hård [21] describes his attempts to cultivate T. pallidum of the Ghent and Nichols strains on embryonated hen eggs, and of the Nichols strain on embryonated goose eggs. Neither dark-field examinations nor mercury or silver impregnation yielded any evidence that T. pallidum is capable of multiplying in eggs. Emulsions of the embryos, when inoculated into rabbits, produced a positive reaction in a single case only. This suggests that spirochetes do not occur in eggs in an ultramicroscopic phase of their life cycle but that occasional spirochetes may survive their

stay in the egg and be reinoculated with their virulence retained. In another study Hård [22] attempted to cultivate virulent T. pallidum in media containing growth factors from plants, namely, hetero-auxin (indole-3-acetic acid), filtered tomato juice, and pieces of raw potato. Each of these substances was added, in separate series, to a basal medium consisting of peptone, agar, dextrose, meat juice, and electrolytes. Growth of avirulent T. pallidum was obtained for several weeks in the medium to which potato had been added.

It was shown in previous communications (Eagle and Steinman, 1948; Steinman and Eagle, 1950) that the nonpathogenic Reiter strain of treponeme can be cultivated on a medium consisting of three amino acids (arginine, cysteine, and phenylalanine), 1 vitamin (pantothenic acid), glutamine, sodium acetate, and crystallized serum albumin, supplemented with a small amount (0.01%) of an enzymatic casein hydrolysate (Amigen). In this study Steinman, Eagle, and Oyama [23] have found that the latter is replacable by a pool of amino acids together with a number of other growth factors. On the addition of this supplement to the above basal medium, one arrives at a medium which is reproducible and which, except for the necessary presence of crystallized serum albumin, is chemically defined. The medium contains amino acids, vitamins, purines, pyrimidines, carbohydrate, inorganic ions, and crystallized serum albumin and no longer requires supplementation with an enzymatic casein hydrolysate. They [24] have also determined the amino acid growth requirements of the Reiter treponeme. The organism requires 13 amino acids, a single pyrimidine, and large amounts of ammonium ion. The ammonia could not be substituted for by any of the amino acids, purines, or pyrimidines studied but could be replaced by glutamine. Oyama, Steinman, and Eagle [25] have found that crystallized serum albumin has a dual role in the cultivation of the Reiter treponeme. It contains a lipid which is the essential growth factor, and the protein itself serves only to bind and detoxify the essential lipid.

Recent studies on the effect of hexachlorophene soaps in reducing resident bacterial populations on the skin interested Keller and Morton [26] to study the quantitative treponemecidal effect of soaps. Nichols, Reiter, and Kazan, three cultivatable strains of treponemes, were tested for their susceptibility to Dial soap, a bar soap stated to contain 2% hexachlorophene (G11), and Ivory soap, an example of a nonmedicated soap. One-half milliliter portions of eight-day-old cultures of these strains were added to 0.5 ml. of freshly prepared soap solutions. These medication tubes were agitated for a short while to insure complete mixing. The medication was room temperature. At intervals of 5 and 10 minutes 0.2 ml. of the medication suspension was transferred to 10 ml. of culture medium. After nine days' incubation at 37 C. all tubes were checked for growth by dark-field microscopy. Suitable bacteriostatic and dilution controls were done. The results showed that the cultivatable treponemes are very susceptible to the action of soaps. There was no significant difference between the soap containing 2% hexachlorophene and the nonmedicated soap. All strains were killed by five minutes' exposure to soaps in dilution of between 1 : 1000 and 1 : 5000, which is 80 to 400 times more dilute than the soap in a good lather.

Turner and Hollander [27] studied two strains of treponemes isolated from cases of endemic syphilis in Bosnia. After considerable study they concluded that these two strains (Bosnia A and Bosnia B) belong to the general group of strains com-

monly designated as T. pallidum and that the response to therapy of patients with endemic syphilis should follow that observed in patients with venereally acquired syphilis.

### EXPERIMENTAL SYPHILIS

One obvious phenomenon this year is the dearth of studies dealing with experimental syphilis. Borel [28] has presented a new technique for the production of early syphilitic acute orchitis in rabbits. Although he found that 15 daily intramuscular injections of mercury succinimide and 15 daily administrations of potassium iodide by stomach tube were inadequate to cure early rabbit syphilis, Kolmer [29] found that both of these drugs showed pronounced synergistic or additive activity when administered at the same time as penicillin G. procaine. According to Levaditi and Vaisman,[30] the association of liposoluble bismuth and oxytetracycline (Terramycin) in experimental syphilis is far from equaling the combination of bismuth and penicillin.

### IMMUNITY IN SYPHILIS

The publications dealing with immunity in syphilis during the past year have not added a great deal to existing knowledge. For example, Krantz [31] asks whether syphilis is curable and comes to the long-well-known conclusion that syphilis is not curable in the bacteriologic sense. Other studies deal with superinfection; the effect of partial immunity on the dissemination of infection in experimental syphilis; comparative study of syphilitic antibodies in blood, bone marrow, and blister fluid; criteria of infection and cure in yaws, and immunologic relationships of T. pallidum and Borrelia anserina.

*Mechanism of Superinfection in Experimental Syphilis; Immunologic Relations Between the Strains of T. Pallidum.*—Vaisman [32] points out that if one reinfects a rabbit cured of testicular or scrotal lesion of syphilis new local lesions do not appear if the reinfection is made with the same strain and at least three months after the first infection. On the other hand, when reinoculation is carried out with a heterologous strain positive results often occur as if there were a local "chancre immunity" of the rabbit in place of the generalized immunity which occurs in man. Vaisman reviews the literature on this point and reports an experiment of his own, as follows: Twenty-nine rabbits were inoculated with the Nichols or Ghent strain of T. pallidum, the inoculation being carried out by the scrotal route. The initial inoculation resulted, after the usual incubation period, in a characteristic syphiloma. These rabbits were then reinoculated with a heterologous strain by the same route, without having been given any treatment for the first infection. Of 14 rabbits which were first infected with the Ghent strain and were then challenged with the Nichols strain at intervals ranging from 60 to 442 days after the first inoculation, only one rabbit developed a chancre in response to the reinoculation. On the contrary, of 15 rabbits first infected with the Nichols strain and later challenged (without treatment) with the Ghent strain at intervals ranging from 82 to 170 days after the first inoculation, 11 developed second syphilomas. The author concludes that the success of superinfection depends on the immunizing power of the originally infecting strain. He feels that the Ghent strain possesses this power to a greater extent than does the Nichols strain.

*Effect of Partial Immunity on the Dissemination of Infection in Experimental Syphilis.*—In an attempt to determine the effect of partial immunity on the dissemi-

nation of T. pallidum in the syphilitic rabbit, Waring and Fleming [33] treated rabbits with penicillin 50 days after infection and four weeks later made intradermal reinoculations of a small number of treponemes. Tissue transfers were then made two to six months after reinoculation. None of these partly immune rabbits yielded positive popliteal lymph node transfers during the second month after the reinfecting injection, and transfer after four and six months failed to demonstrate infection of lymph nodes in an appreciable number of the rabbits. The authors conclude that incomplete immunity may delay or impair demonstrable involvement of lymph nodes and perhaps other tissues, notwithstanding development of new primary lesions following reinoculation. They point out that lymph node transfer as an index of infection may be unreliable in partly immune rabbits.

*Comparative Study of Syphilitic Antibodies in Blood, Bone Marrow, and Blister Fluid.*—A study was carried out by Binazzi [34] on blood, bone marrow, and vesicular fluid of 71 syphilitic subjects. The blood was obtained from a vein, the bone marrow from the sternum, and the vesicular fluid from the vesicles produced by the application of cantheridin plaster on the skin. The amount of antibodies (syphilitic) was lower in the blister fluid than in the venous blood in primary and secondary syphilis. It was nearly the same in old syphilis. An eightfold amount of antitreponemic antibodies was found in the vesicular fluid of 33 persons with seronegative late syphilis. Bone marrow antibodies parallel those in venous blood. Antitreponemic antibodies were present in 5 of 10 seronegative subjects in the late phase of the disease.

*Fractional Analysis of Reiter Antigen.*—D'Alessandro and Dardanoni [35] have pursued further their previous studies which indicated the presence of four separate and distinct antigenic components in the Reiter strain of cultured T. pallidum. These four antigens are a treponeme-specific protein antigen, the ubiquitous tissue lipid antigen, a treponeme-specific polysaccharide antigen, and an antigen related to, or identical with, the organ-specific lipid antigen of the brain. The present work investigates further the characteristics of the protein antigen. This is prepared by cryolysis (repeated freezing and thawing) of the treponeme and precipitation with ammonium sulfate. The antigen was designated ATPS (soluble protein antigen of the Treponema). Two-dimensional paper chromatography revealed the presence of many amino acids in the antigen. The authors demonstrated that ATPS is not associated with the ubiquitous lipid antigen or with the polysaccharide antigen. Intravenous injection of ATPS into rabbits caused the formation of antibodies which reacted in vitro with ATPS but which did not react with lipid or polysaccharide antigen. When syphilitic sera were tested with this antigen, a curious prozone phenomenon was demonstrated. Reaction in the complement fixation test was greater when ATPS was diluted to 1:32 to 1:64 then when it was concentrated. In comparing the ATPS antigen in various stages of syphilis with cardiolipin and a suspension of Reiter-strain treponemes, the authors found positive reactions with ATPS less frequent in long-standing cases or after treatment. In congenital syphilis, some patients reacted only with lipid antigen and others only with ATPS. In yaws results were similar. In leprosy ATPS gave fewer positive reactions than the other antigens. The authors consider ATPS an antitreponemal antigen but do not feel that it is identical to the antigen which reacts with Treponema-immobilizing antibody. In a study of the curative dose of peni-

cillin in rabbits infected with yaws, McLeod and Magnuson [36] estimated the 50% curative dose to be approximately 16,000 units per kilogram when the preparation employed was penicillin G procaine in peanut oil with 2% aluminum monostearate, given in four equal daily injections. The authors discovered that negative lymph node transfer could not be relied upon as evidence of cure in the treated rabbit with yaws, in that many of the lymph-node-transfer rabbits which failed to develop lesions were proved to be infected by dark-field examination of the clinically negative injected testes or by subinoculation of testicular fluid to normal rabbits. It is suggested that the yaws spirochete possesses a relatively low degree of invasiveness for the rabbit lymph node. Saurino and DeLamater [37] have demonstrated both agglutination and immobilization of Bor. anserina, the causative organism of avian spirochetosis, by immune chicken serum. They have also demonstrated that cross reactions occur between Bor. anserina and T. pallidum, as evidenced by the fact that both rabbit and human syphilitic serum cause some degree of agglutination of Bor. anserina. These cross reactions suggest the possibility of a common antigen in the two organisms.

### PROGNOSIS

Rosahn [38] has produced perhaps the most outstanding research of the year. Winner of the American Dermatological Association's Prize Essay Contest, he found that syphilitic infection adversely influences longevity. Evidence from vital statistics and clinical surveys indicates that syphilitic persons have a higher mortality than nonsyphilitic persons of similar age, sex, and race. Autopsy studies indicate that fewer syphilitic persons with or without lesions at autopsy survive the age of 70 than do nonsyphilitic persons. Both syphilis prevalence rates and mortality rates from all causes vary according to socioeconomic factors: the better the socioeconomic conditions, the lower the rates. Since it cannot be determined from studies of the human disease whether the decreased longevity of syphilitic persons results from syphilitic infection per se or from the socioeconomic conditions that foster high syphilis-prevalence rates and high mortality rates from all causes, a study of syphilis in mice was undertaken. A genetically homogeneous population of C57 black mice were employed. Of littermate pairs of the same sex, one was inoculated intraperitoneally with virulent treponemes and the other with saline solution. Feeding, watering, and environmental temperature were standardized. Sixty-nine pairs of females and 71 pairs of males were available for analysis. The mean age at death of the control male and female groups was significantly greater than the mean age at death of the syphilitic groups of the same sex. The proportion of nonsyphilitic mice that outlived their syphilitic littermates was significantly greater than the proportion of syphilitic mice that outlived their control nonsyphilitic littermates. More control mice of either sex lived to be 700 days or older than did syphilitic mice of the same sex. It is concluded that syphilitic infection in mice exerts a deleterious effect on longevity. Although the mechanism producing this effect is conjectural, it is suggested that syphilis depresses resistance to other fatal diseases. If the same mechanism is operative in man, and there is reason to believe that it is, then syphilis by itself, exclusive of modifying socioeconomic factors, exerts an adverse influence on the life span of the human host.

DIAGNOSIS OF SYPHILIS

Aside from the growing interest in the treponemal immobilization test (see below), there has been considerable interest in other diagnostic procedures, chiefly serologic. Rottmann [39] has employed the repeated injection technique of the luetin reaction in a number of phases of syphilis, especially in the so-called focal reaction, late congenital syphilis, and endemic syphilis.

SERODIAGNOSIS

In the field of serodiagnosis the newer developments have been summarized by Pautrizel [40] and by Nelson.[41] Krag,[42] serologist of the World Health Organization, emphasizes the need for and steps being taken to standardize the serodiagnosis tests. The work planned and undertaken by the World Health Organization is designed to minimize some of the difficulties encountered by laboratories, but much depends upon the help it receives from them in the way of collecting information and performing experiments. Hussels [43] likewise makes pertinent suggestions for standardization of serologic performance. Numerous other studies dealing with the technical as well as the clinical aspects of serology bear witness to the continued interest and progress in this field. The problem of biologically false positive reactions to the serologic tests for the diagnosis of syphilis seems well on the way to solution. Perhaps the best presentations on serodiagnosis are those of Moore and his colleagues, from Johns Hopkins University, dealing with the general problem and the specific value of the treponemal immobilization test in determining the falseness or verity of the serological result. An important by-product of the interest in biologic false reactions is the realization that although these reactions may not indicate the presence of syphilis they may forbode the development of a serious medical disease, such as one of the collagen group.

*Changing Concepts in Serodiagnosis of Syphilis.*—Nelson's work [41] has resulted in the discovery of two immunological phenomena which have helped to change the concepts of serodiagnosis of syphilis and of the fundamental nature of the immune mechanisms which function in syphilitic infections. While this work should be discussed under the TPI test, placing it here adds perspective to the relationship of this test to the more routine procedures. Previous work in experimental syphilology had been conditioned by the concept that little could be accomplished in the field of specific serodiagnosis without cultivation of treponemata. This led to attempts to modify techniques for detection of Wassermann reagin, a fruitless pursuit, because it has not yet been possible to identify the antigen against which Wassermann reagin is an antibody and the entire concept of the Wassermann reaction is based on nonspecific principles. During a search to find a synthetic medium which would maintain treponemata, Nelson found the beneficial role of carbon dioxide, pyruvic acid, and certain sulfhydril compounds, and also, if extreme care were exerted in isolating treponemata early in the course of syphilitic orchitis, it was possible to keep T. pallidum actively motile and virulent in vitro in a relatively tissue-free suspension for 8 to 10 days. The isolation of the serum fraction which exerted this beneficial effect was found by Nelson and Rice to be a crystalline compound, $C_{12}H_{22}O_{10}H_{20}$. Nelson then turned his attention to determining whether specific antibody could be shown to exert any measurable effect on T. pallidum in vitro. This resulted in the discovery by Nelson and Mayer of the so-called treponemal immobilizing antibody. Early experiments showed that

this antibody was separate and distinct from Wassermann reagin. It appeared also that the antibody played a role in immunity. This was elaborated by Turner and Nelson, who found an approximately direct relationship between the titer of antibody in the serum and the degree of resistance to reinoculation. In spite of the findings, no definite answer can be given to the question of the relationship between the immobilizing antibody and immunity. Certainly the findings of Magnuson and his group indicate that immobilizing antibody may not be directly associated with immunity. The treponemal immobilization procedure (TPI) has been performed in the identification of strains of T. pallidum in experimental animals. Treatment also affects the immobilizing antibody titer in human beings, causing a decline in patients with early syphilis but not in patients with late syphilis. This fact raised the question as to whether treatment is curative in late syphilis or whether, treatment having destroyed the spirochetes, the tissues have been sensitized and continue to produce antibodies even though the organisms are eliminated or whether, the micro-organism being destroyed, there is still adequate soluble antigen in the tissue of the host to stimulate antibody formation. The test has brought out the possibility of Wassermann-negative asymptomatic relapse. The qualitative TPI test may give positive reactions up to 40 years after treatment of patients with proved late syphilis. The test has also been applied to the solution of certain difficult clinical problems, that is, in the problem of nonspecific (biologic false) positive seroreactions. This test has been especially useful in the case of the positive seroreactions in leprosy as well as in the general problem in two distinct patient populations. Nelson also studied in vitro phagocytosis of T. pallidum. He demonstrated (1) the ability to obtain from the rabbit tissue-free suspensions of organisms which were also free of small amounts of antibody and (2) the use of indirect techniques for measuring antibody action, rather than the staining of leucocytes used in classical phagocytosis experiment. More details of this work are given in other papers (below).

In spite of the great advances made by the TPI test, the routinely used serologic procedures continue to perform a most useful service. Hinton [44] rates the serologic tests for syphilis as the most effective means of detecting the disease. They are valueless in (1) determining the infectiousness of the disease and (2) in appraising the severity of the infection and (3) they are unreliable in estimating the effect of treatment in such a large number of cases that for individual patients no dependence can be placed on them either in prognosis or determining cure. Kampmeier,[45] in a careful review, reminds the practitioner that although the serologic tests are of great value in various aspects of syphilis diagnosis they have definite shortcomings because of false reactions. He decries prediagnostic therapy of syphilis because it is poor medicine and may induce serious psychoneuroses and anxiety states resulting from a diagnosis of syphilis. Rein and Kostant [46] evaluate the place of serum tests in the diagnosis of syphilis in the newborn and the infant. They state that three types of antibodies may be passively transferred from the mother to the fetus: (*a*) syphilitic reagin, detected by standard lipidal serologic tests for syphilis; (*b*) false-positive reagin, also detected by means of the treponemal immobilization test, and (*c*) antitreponemal antibody, detected by means of the treponemal immobilization test. The serologic diagnosis of prenatal syphilis depends on observation of (*a*) persistent and/or rising quantitative serologic titers of syphilitic reagin and (*b*) persistent and/or rising quantitative serologic titers of

treponemal immobilizing antibody. The authors believe that too many newborn infants with passive transfer of reagin are subjected to needless treatment and that many syphilitic children with persistently positive serologic reactions following adequate antisyphilitic treatment are needlessly retreated.

For field surveys, according to Kvittingen and his co-workers,[47] a rapid method for carrying out the serologic test for syphilis was developed by the World Health Organization Venereal Disease Demonstration Team in India. The method, based on the Meinicke slide test, reduced the clotting time by exposing the samples to the sun or by keeping them in a water bath at 37 C. With this method it was possible to collect and test samples and treat those with positive tests in one day. Results obtained on seven surveys were successful. All 1,431 samples taken were retested with the same batch of Meinicke antigen, and 1,421 were tested with VDRL. The agreement between the field and laboratory Meinicke tests was 98.5%. The new method proved to be the most appropriate procedure for use in underdeveloped areas with a high syphilis rate.

*Anticomplementary Reactions.*—The anticomplementary reaction is the inhibition of hemolysis in the antigen-free mixture of serum and complement used as control in complement-fixation tests. Such a serum is not suited for a Wassermann or a Kolmer test. If an anticomplementary reaction is noted and the complement-fixation test repeated in the next day or two with fresh serum, proper ingredients, and correct technique again results in the anticomplementary reaction, the reaction can be considered "intrinsic" (or "endogenous" or "autonomous" or "natural"). If the reaction is caused by faulty laboratory technique and can be avoided by correct laboratory technique, it is called "extrinsic" (or "exogenous" or "artificial"). Lighter [48] reviewed the charts of 144 patients who at one time or another had had anticomplementary reactions (probably all were of the intrinsic type). Of these reactions, 88.2% occurred in syphilitic persons, for 25.9% of whom the diagnosis was congenital syphilis. Congenital syphilis participated in anticomplementary reactions about seven times as often as would be expected if anticomplementary reactions were distributed equally among cases of congenital and acquired syphilis. Lighter introduces a new concept, namely, the "repeatedly anticomplementary reaction," which denotes that the quality of the serum causing anticomplementary reactions is not transient but lasts for at least many weeks, usually several months or even years. Of "repeatedly anticomplementary reactions," 96.5% occurred in syphilitic patients, 38.2% of whom had congenital syphilis. Congenital syphilis participated in the "repeatedly anticomplementary reactions" 10 times as often as expected. Because of the heavy participation of syphilis in general and of congenital syphilis in particular in the anticomplementary reactions, thorough examination and serologic follow-up of persons with anticomplementary reactions should be made, especially of those with "repeatedly anticomplementary reactions."

*Survey of Intrastate Serology Evaluations.*—In 1951 a survey was conducted to determine the current status of intrastate serology evaluations.[49] The extent and duration of these programs in 36 states, 2 territories, and 2 cities, New York and St. Louis, are summarized in a table. The table gives details of the number and type of laboratories participating, the number of specimens distributed, and the number of years the program has been in progress. In 30 of the states, the Venereal Disease Research Laboratory was used as the reference or control labora-

tory. All the 40 state laboratories "offer an educational program and consultive service to laboratories desiring or needing assistance." Judging by the appended notes on the questionnaires, the intrastate serology programs are being increasingly recognized as an important educational activity.

*Plurality of Antibodies in Syphilitic Serum.*—Puccinelli [50] had previously described three antibodies in serum of syphilitic patients. They are: TL, antitreponemal antibody TL; TS, antitreponemal antibody TS, and L, antilipoid antibody L, or flocculating antilipoid antibody. The clinical and serological investigations which he and his colleagues have been carrying out for more than eight years lead to the belief that the presence of TL in the serum indicates a persistence of the Treponema in the organism. Whether this finding is the proof of an actual lesion can only be ascertained by a thorough clinical examination. In any case, the finding should always be interpreted as indicating the need for accurate and painstaking supervision of the patient. The presence in the serum of L alone, without the antitreponemal antibodies, is a finding that should always be considered very conservatively, as it constantly tends to disprove the existence of syphilis in the active stage; it may either indicate an aspecific proteidopoietic alteration or may represent, in recently-treated congenital syphilis, a mutation of the normal proteidopoeisis in a particular section. Investigations now in progress may differentiate the complement-fixing antilipoid antibodies from the flocculating ones, and, to prove their respective clinical significance, the great importance of the persistence of TS in the serum of treated syphilitics must be emphasized. A systematic serological analysis of the different diagnostic antibodies in persons with syphilis proves their practical usefulness in diagnosis, prognosis, and therapy. Everyday experience indicates that in the serology of syphilis, as in the immunochemistry of so many other infectious diseases, the protein antigens are the most active in the production of their "antigenic power" but also in view of the specificity of their reactions. The extensive statistical data supplied by Italian serologists lead to the belief that TL antibody (antiprotein) is the diagnostic antibody that more than any other constitutes an immunochemical mark indicating the presence of Schaudinn's pathogenic Treponema in the organism. Nevertheless, a thorough serological investigation of the syphilitic should always include a careful examination of the full range of the diagnostic antibodies (and, if possible, of some of the immune-antibodies) in the serum, as only a comprehensive and well-balanced understanding of these elements can provide a clear and definite diagnostic, prognostic, and therapeutic judgment of syphilitic infection.

*Reaction of Wassermann Antibody.*—Geiduschek and Doty [51] summarized their report as follows:

The hapten-antibody system for which the antibody is human Wassermann antibody and cardiolipin the hapten, has been investigated by the monolayer technique. The experimental study reported here has centered about the demonstration that the specific reaction can be detected by this method, due to the different *p*H dependence of the rate of interaction of a hapten monolayer spread at an air-water interface with its substrate containing homologous antibody or normal human γ-globulin. The results are interpreted to mean that a monolayer of pure cardiolipin is not haptenic toward Wassermann antibody but that mixed films of cardiolipin-cholesterol and cardiolipin-lecithin do undergo specific reactions. The possibility that other polar molecules, when mixed with cardiolipin, also complete the haptenic requirements of Wassermann antibody, is discussed briefly.

*Antisheep Amboceptor.*—Muraschi and her co-workers [52] studied the effectiveness of five methods of antisheep amboceptor production in rabbits in terms of the hemolytic titers produced. A modification of the method of Ulrich and McArthur, in which 10% cells in serum were injected intravenously and the rabbits bled on the 25th day, was determined to be the most effective method.

*Antigen.*—Considerable study of the problems relating to the antigen for the various serologic procedures used in serodiagnosis have yielded many reports but with little new data. By far, the greatest interest is still centered about the cardiolipin antigens.

*A Modified Technique for Antigen Delivery.*—Ernst and his co-workers [53] have developed a procedure for delivering antigen in which the size of the drops, and therefore the actual quantity of antigen, can be accurately duplicated, not only from test to test but from day to day. The technique involves the use of a 2 cc. syringe without the plunger, fitted with a 21 gauge 1½ in. (3.75 cm.) medium-level hypodermic needle, attached to a ring stand and clamp at an angle which permits delivery of 60 drops per cc. of antigen emulsion.

*Antigen Suspensions Made at Various Temperatures.*—In a laboratory with a "room temperature" of 22.4 C., Fugazzotto [54] found it possible, under controlled conditions, to prepare antigen suspensions under conditions of temperature ranging from 15.3 C. to 37 C. With the use of these antigens (brought to a room temperature of 22.4 C.) data were obtained showing that the microscopic appearance and the sensitivity of a flocculation test antigen suspension (VDRL) are in a degree determined by its temperature at the time it was made. This report is offered as an indication that environmental temperature is one of the factors contributing to wide variations in serologic test performance.

*Comparison of Two Commercial Meinicke Antigens.*—In the comparison of two commercial Meinicke antigens, Ghorpade [55] studied 265 specimens. Except for a few, selection of the 265 samples was confined to those which had reacted negatively in routine examination with the slide modification of the Meinicke test. Swedish Astra antigen and French Meditec antigen were used. Three different saline solutions were used, which were stored in bottles until the tests began. The Meditec antigen proved to be more sensitive than the Astra, producing a larger number of positive reactions and stronger reactions in samples which reacted negatively to both antigens. Both antigens were more sensitive when prepared with the test saline solutions than with routine saline solution, with the exception of the Meditec antigen mixed with saline solution from one of the test bottles.

*Cardiolipin Antigen.*—Cardiolipin antigen is considered in a series of reports by Lundbäck * dealing with the effect on the activity of cardiolipin-lecithin-cholesterol antigen of variation of the procedure for diluting and combining the separate components and comparison of some properties of unpurified and cardiolipin-lecithin-cholesterol antigens. Schmidt [61] showed that the quantitative relations of syphilis at different stages between Wassermann's complement-fixation test as modified by Mørch (WR-M; Mørch's Wassermann-complement-fixation reaction), a complement-fixation test after the same technique using cardiolipin (C-WR-M), and Kahn's standard test (KR) have been investigated. The three different tests were used to examine 3,980 blood samples. The sera were divided into two groups:

* References 56-60.

Group A from patients with syphilis, clinical or anamnestical, and Group B from patients without syphilis. Sera from patients with syphilis were subdivided into three groups: (1) from patients with primary syphilis (SI), (2) from patients with tertiary syphilis (SIII), and (3) from all other syphilitic patients ("rest"). No distinction was made between treated and untreated cases of syphilis. The results of the examination of sera from Group B will be published later. A brief account is given of the technique of the complement-fixation tests. C-WR-M needs more complement than WR-M to obtain the same degree of hemolysis. (For further details see Schmidt, H.: Cardiolipin Antigen: I. A Qualitative Examination of Sensitivity and Specificity, *Brit. J. Ven. Dis.* **27**:23-33 [March] 1951.) Qualitative estimation shows that WR-M is significantly more often positive in Group SI than KR, which again is significantly more often positive than C-WR-M. In the "rest" group, KR is significantly more often positive than either WR-M or C-WR-M, whereas no difference in the number of positive reactions can be demonstrated between the two complement-fixation tests. In Group SIII, KR is significantly more often positive than WR-M, whereas no significant difference can be demonstrated between KR and C-WR-M or between WR-M and C-WR-M. Quantitative estimation indicates that no difference in potency between WR-M, C-WR-M, and KR can be demonstrated in the "rest" group. In Group SI, WR-M is significantly stronger-reacting than C-WR-M, the difference between the two complement-fixation tests being greater on the lower than on the higher potency level. There is no difference between C-WR-M and WR-M in Group SIII. There is no significant difference between KR and C-WR-M in Group SI. C-WR-M is significantly stronger-reacting than KR in Group SIII. Finally, WR-M is significantly stronger-reacting than KR in Group SI, whereas no difference can be demonstrated with certainty between KR and WR-M in Group SIII. The investigations are discussed, and an attempt is made to explain the fact that the relations between the different reactions are not the same in primary syphilis (Group SI) as in other stages of syphilis. Hasselmann [62] found cardiolipin antigen to excel over all other available antigens. Merklen and Berthaux [63] call attention to the fixation of nonspecific protein by cardiolipin antigens in normal and syphilitic serum and the role this may play in the mechanism of production of biologic false positive reactions in the serums of certain nonsyphilitic persons. An investigation into the use of cardiolipin antigens with a view to adapting them to the Whitechapel Wassermann technique has been undertaken by Orpwood Price.[64] He found that, as a result of an experiment to determine the optimum conditions for the adaptation, anticomplementary effects would be avoided if the cardiolipin antigen would be made to the formula cardiolipin 1, lecithin 1, cholesterol 10, at a unit strength of 0.05%. Kolmer, Lynch, and Black [65] performed four tests on the serums of 412 persons. Tests were quantitative Kolmer complement-fixation tests conducted with 0.03-0.05-0.3 and 0.3-0.05-0.6 cardiolipin antigens and improved Kolmer antigen and the Kline standard flocculation test conducted with the cardiolipin antigen marketed by the LaMotte Chemical Company. Negative reactions were observed on 210 serums in all four tests. Both cardiolipin antigens employed in the Kolmer tests gave apparently true positive reactions with 164 (39.8%) of the serums. True positive reactions were observed on 149 serums in tests conducted with improved Kolmer antigen. Of the 15 persons whose serums yielded positive Kolmer complement-fixation reactions with the two cardiolipin antigens

but negative reactions with improved Kolmer antigen, 12 had been treated for syphilis. This indicated the somewhat superior sensitivity of cardiolipin antigen in the Kolmer complement-fixation test. Klein and his co-workers [66] observed significant differences with the Kline cardiolipin slide test for syphilis when the slides were rotated on each of three mechanical rotators operating at 56, 182, and 301 rpm, respectively. Sensitivity of the test varied inversely with the rate of rotation. A study, from Gadels Institute, Bergen, by Vogelsang [67] presents the results of parallel complement-fixation tests on 10,000 sera by a modified Eagle technique, using three antigens (*a*) cholesterolized alcoholic extract of ox heart muscle which had been treated with acetone and ether and was used at a titer of 1:120; (*b*) cardiolipin antigen (cardiolipin 0.0175%; lecithin 0.0875%; cholesterol 0.3%) used at a titer of 1:130; (*c*) sitolipin antigen (sitolipin, a phosphatidic acid prepared from wheat embryo, 0.05%; lecithin 0.3%; cholesterol 0.9%). This was diluted as for flocculation test antigen (Uroma, E.: Sitolipin Antigens in the Serodiagnosis of Syphilis, *Acta dermat.-venereol.* [Supp. 24] **31:**184-188 [Sept. 4-10] 1950) and was further diluted 1:3 for use in the complement-fixation test.

Seven hundred ninety-three sera came from patients with evidence of syphilis. Positive results were obtained from 540 (61.8%) of these with the crude extract antigen, from 548 (69.1%), with the cardiolipin antigen, and from 537 (67.7%) with sitolipin antigen. In 19 cases of primary syphilis, the crude extract antigen was positive in 13 and the cardiolipin and sitolipin antigens in 10 cases each. In sera from other stages of untreated syphilis and from treated patients, the cardiolipin antigen gave the most positive results.

In the group of 9,207 patients who were considered to be nonsyphilitic, the crude extract antigen gave 80 (0.87%), the cardiolipin antigen 63 (0.69%), and the sitolipin antigen 60 (0.65%) positive results. It is concluded that it is more by their specificity than by their sensitivity that the complex phosphatidic acids mark an advance in the serology of syphilis.

*Standardization of the Wassermann Test Using Preserved Complement Titrated to 50% Hemolysis.*—Coleman [68] presents a modification of the Fairbrother-Maddocks method for the Wassermann test employing 50% hemolysis as the end-point of the complement titration. The titration is carried out photometrically. The amboceptor titration has been investigated, and a corresponding elaboration has been found to be unnecessary. The use of a complement preserved by Richardson's method at a predetermined fixed titer enables standard results to be obtained irrespective of variations in the behavior of the hemolytic system and allows the day's tests to be begun without waiting for the working out of the complement titration.

*Observed Pattern of Entrance into Seroreactivity Among Patients with Untreated Primary Syphilis.*—Cutler and his co-workers [69] studied the results of a battery of serologic tests performed at weekly intervals in 33 patients with seronegative primary syphilis who were permitted to progress to seropositivity without treatment. The battery of tests included the Mazzini flocculation, Kahn standard, Kolmer with beef-heart antigen, Kolmer with cardiolipin-lecithin antigen, and two VDRL slide flocculation tests, using antigens set at different levels of sensitivity. With few exceptions, the most sensitive test, the Mazzini flocculation, became positive first. The Kahn, the above-standard VDRL, and the cardiolipin-lecithin

Kolmer tests showed somewhat lower levels of sensitivity, and the regular Kolmer and the standard VDRL tests were least sensitive. However, the authors found that in some patients the most sensitive test became positive later than the least sensitive and hypothesized that the procedures using crude lipoidal antigens may be testing for substances other than reagin. Within 35 days after the patient became seropositive with any one of the tests, all tests employed in this study were positive.

*Patients with Negative Kahn Standard Tests and Reactive VDRL Slide Tests for Syphilis.*—Olansky and his associates [70] state that during the past few years physicians and laboratory directors have criticized the VDRL slide test as too sensitive, inasmuch as it shows positive or doubtful reactions in many sera which are negative with the Kahn standard test. In an effort to evaluate whether these positive tests are due to high sensitivity or to lack of specificity, over 3,000 VDRL-positive Kahn-negative patients were studied by means of history, physical examinations, and serologic and spinal fluid tests. The treponemal immobilization test was not used, and the criteria for diagnosis are not described. Forty-three per cent were diagnosed as having adequately treated latent syphilis, 46% as having inadequately treated latent syphilis, and 6.4% as having neurosyphilis. In addition, primary syphilis, congenital syphilis, benign late syphilis, central nervous system syphilis, and cardiovascular syphilis were diagnosed in a smaller number of patients. Only 51 patients (1.6% of the total) were diagnosed as nonsyphilitic. This study indicates clearly that VDRL enjoys a higher sensitivity than the Kahn standard test, with no significant increase in the incidence of false positive reactions.

*Comparative Value of Various Serologic Procedures.*—The VDRL Slide Flocculation Test: During a 10-month period Eaton [71] observed 194 patients having positive reactions with the VDRL slide test and 2 patients with seronegative primary syphilis. The test was found to be most valuable as a presumptive test for syphilis. The simplicity of technique makes it ideal for performance of large numbers of serologic tests in a short period of time. The quantitative VDRL test is useful in the follow-up of treated patients. Levitan and his co-workers [72] performed Kahn, Kolmer, Mazzini, and VDRL slide tests on 438 children between the ages of 6 and 16 years, resident in the National Orphanage of Guatemala. Three children were diagnosed as syphilitic. In addition, 89 children showed seroreactivity by one or more of the tests employed. The authors believe that these 89 children were biologic false positive reactors rather than syphilitics. Inasmuch as the Kolmer and the VDRL slide tests showed a smaller number of positive reactions in this group than did the Mazzini and Kahn procedures, the authors feel that the former tests are less likely to give biologic false positive reactions and suggest that they are preferable for routine testing. We believe that discrepancy between tests, such as was demonstrated here, results from variations in the sensitivity of these tests in a given laboratory. He has seen many instances in which Test A is more sensitive than Test B in one laboratory and less sensitive than Test B in another laboratory. For this reason, he cannot feel that the conclusions reached in this paper are applicable outside of the laboratory where the testing was carried out.

The Rein-Bossak Microflocculation Slide Test: The Rein-Bossak microflocculation slide test was carried out by Madsen [73] in 296 serums from patients with evidence of syphilis and in the serums of 8,042 patients without evidence of syphilis. The VDRL tube-flocculation test, Meinicke Clarification Test II, and a

complement-fixation test with cardiolipin-lecithin-cholesterol antigen were done for comparison. Results showed that the Rein-Bossak test was not superior to the other tests. The author recommends that this test not be used alone. Comparative examinations were made by Hesselberg and Madsen [74] with the Mazzini and the Rein-Bossak microflocculation slide tests on 5,953 sera received for routine serodiagnosis of syphilis. There were 275 sera among them from known cases of syphilis. While both tests had equal specificity, the Mazzini procedure seemed to have a slightly better sensitivity.

The Rappaport-Eichhorn Flocculation Test: According to Hesselberg,[75] comparative examinations of 7,300 serums at Gade's Institute, Bergen, have shown that the Rappaport reaction is more sensitive than a complement-fixation reaction with crude antigen, a complement-fixation reaction with cardiolipin antigen, Meinicke Clarification Reaction II, and the VDRL tube-flocculation test. It showed somewhat less specificity than the two complement-fixation tests, while it was equal with the two other flocculation reactions. The difference in specificity between the Rappaport and VDRL tests was only 0.02%.

Small-Quantity Blood Tests: In an annotation in Lancet [76] the results of studies of the Venereal Disease Section of the United States Public Health Service on various microserologic tests for syphilis are reported. These data have been detailed in previous reviews.[1] Dahr [77] used the original method of Chediak with satisfactory results from the standpoint of convenience and availability. Schrader and Kurze [78] also successfully employed the Chediak original extract in a microrapid test procedure on 1,954 serums. Along these same lines, Stübben [79] subscribes to the value of the microcomplement-fixation reaction in the diagnosis of syphilis.

New Tests: Botanical test. Macht [8] discovered that syphilitic sera dissolved in plant physiological saline and studied by his phytopharmacological methods on vernalized, or yarovized, seedlings produce a characteristic phytotoxic effect, inhibiting the root growth. This action is a quantitative one and compares well with the titer of syphilitic sera obtained in the serological laboratory. A similar phytotoxic effect is produced in syphilitic spinal fluids. These reactions have been found useful in diagnosis and in following the effect of treatment with antibiotic drugs.

New hemolytic serologic reaction. Cohen [81] described in a preliminary report a hemolytic reaction employing phospholipid material with hemolytic properties, in which complement and amboceptor are not required. The reaction is based on the accepted principles underlying all hemolytic and flocculation tests. The phospholipid used by Cohen was an ether extract of a commercial partially oxidized aged egg-lecithin, which possessed both hemolytic activity and a greater affinity for positive syphilitic sera than for negative sera. Addition of suitable quantities of cardiolipin and cholesterol increases the affinity of the hemolysing material for positive sera without affecting its hemolytic activity.

*Biologic False-Positive Reactions.*—As stated above, the problem of biologic false-positive reactions to the serologic tests for syphilis seems near solution in so far as it is that of having a means (the TPI test) of differentiation of true from false reactions. However, the big problem of the significance of these false reactions has posed a medical enigma which still taxes the ingenuity of the most skillful physician. Once a reaction has been established as falsely positive, it behooves the medical attendant of the patient yielding this result to make the most thorough

search for the cause of the reaction. Although additional data dealing with biologic false-positive reactions will be presented in the section on the TPI test, the most outstanding papers on this problem, by Moore and Mohr,[82] as well as others, are detailed here, since they contain general data on biologic false-positive reaction. In this important contribution to the problem of biologic false-positive reactions in serologic tests for syphilis (BFP), these authors made preliminary observations on the identification of the chronic BFP-reactor by the use of the treponemal immobilization test; on the incidence of such reactions in a particular population group, and on the possible etiologic background, so far poorly defined, of the type of serologic abnormality. Their data suggest that the chronic BFP phenomenon is far from innocuous, as has heretofore been thought. It is often related to and may be the first evidence of serious underlying disease. Collagen disease may be closely related to the chronic BFP phenomenon. If these observations are borne out by further study, an opportunity may be provided better to define the early manifestations and natural history of the collagen disease group. We find the thesis of Moore and Mohr attractive, but it is based on implicit acceptance of the validity of the treponemal-immobilization-test reactions as indicators of the presence of a syphilitic infection. Until such exact correlation has been proved, we can only hope that their thesis will be borne out by further study.

Moore and Mohr [83] compiled a list of the various nonsyphilitic conditions which may produce a biologically false-positive reaction. The approximate percentage incidence represents an average estimate of the incidence of positive serologic tests for syphilis in many reported series. Individual reports vary enormously, depending on the sensitivity of the particular serologic technique employed and on whether serial testing was carried out during and after the particular infection or condition. Finally, and most important, it must be remembered that the incidence of positive reactions recorded in this table includes some persons with syphilis as well as biologically false-positive reactors. In no series so far reported for any condition (except leprosy) have the positive reactors with standard serologic tests been checked with the treponemal immobilization test, and the actual incidence of biologically false-positive reactors is as yet unknown.

The approximate incidence of biologically false-positive reactions is as follows:

| Infections | % |
|---|---|
| Bacterial disease | |
| Leprosy | 60 |
| Tuberculosis, advanced | 3-5 |
| Pneumonia, pneumococcal | 2-5 |
| Subacute bacterial endocarditis | 5 |
| Chancroid | 5 |
| Scarlatina | 5 |
| Spirochetal disease | |
| Leptospirosis | 10 |
| Relapsing fever | 30 |
| Rat-bite fever | 20 |
| Plasmodial disease | |
| Malaria | 100 |
| Rickettsial disease | |
| Typhus | 20 |
| Protozoal disease | |
| Trypanosomiasis | 10 |
| Viral disease | |
| Vaccinia | 20 |
| Pneumonia, "atypical" | 20 |
| Measles | 5 |
| Chicken pox | 5 |
| Lymphogranuloma venereum | 20 |
| Infectious hepatitis | 10 |
| Infectious mononucleosis | 20 |
| common cold | ? low |
| Noninfectious diseases or conditions | |
| Lupus erythematosus | 20 |
| Lupus erythematosus (disseminated or discoid) | 20 |
| Rheumatoid arthritis | 5 |
| Blood loss, repeated (as in multiple donations for transfusions) | ? low |
| Pregnancy | ? low |

Moore and Mohr, on the basis of their considerable experience, express the epidemiological opinion that in certain population groups in the United States (especially in white persons of relatively high socioeconomic status in the northeastern, northern, and northwestern states) at least half of seropositive reactors discovered in mass blood-testing programs do not have syphilis at all but do instead have biologically false-positive reactions. Increasing knowledge of the biologically false-positive phenomenon has permitted its differentiation into two types, which, for lack of better names, may be designated as "acute" and "chronic."

Acute biologically false-positive reactions are characterized by the fact that they occur during or shortly after a wide variety of unrelated nonsyphilitic infections or conditions and that they disappear spontaneously within a few days, weeks, or months (not more than six months) after recovery. "Acute" reactions are usually associated with a bacterial, viral, plasmodial, or Rickettsial infection.

Chronic biologically false-positive reactions are marked by the fact that reagin persists in the blood over many months or years, perhaps even for a lifetime. So far, the only infectious disease known to produce chronic biologically false-positive reactions in a high proportion of cases is leprosy. It is also clear that a proportion (not exactly defined) of patients with discoid or disseminated lupus erythematosus may show chronic biologically false-positive reactions. Aside from this, knowledge as to their cause is still meager. The etiologic background of the chronic biologically false-positive phenomenon is under study at the Johns Hopkins Hospital clinic, by means of a long-term clinical follow-up of such patients. Only preliminary results are so far available, but these indicate that the biologically false-positive reaction is not innocuous, to be dismissed lightly, but is often, perhaps usually, a manifestation of serious underlying disease. Outstanding among the conditions so far identified in a substantial proportion of biologically false-positive reactors are the collagen diseases, such as disseminated lupus erythematosus, periarteritis nodosa, rheumatoid arthritis and rheumatic fever, and sarcoid.

The clinical recognition of biologically false-positive reactions is a time-consuming and laborious procedure. For any suspected biologically false-positive reactor, epidemiological investigation (as a minimum, routine serologic testing) of familial and sexual contacts is essential, in order to verify the patient's statement of lack of exposure to the possibility of congenital or acquired syphilis. In all suspected chronic biologically false-positive reactors, the spinal fluid must be demonstrated to be normal, since false-positive serologic reactions in the spinal fluid (in contrast to blood serum) do not occur except in certain easily recognized neurological disorders. The value of the TPI test in determining the verity of the positive reactions is discussed below.

Mechanism of Biologic False Positive Reactions: Stout and his colleagues [84] discuss the relationship of biologic false-positive serological reactions to the tests for syphilis and the protein content of serum as well as to the albumin and globulin content. They could find no significant correlation.

Neurath Test: On the basis of a large-scale study of the Neurath inhibition phenomenon in the serodiagnosis of syphilis, Falcone and her associates [85] concluded that the Neurath procedure added no significant information to that given by the standard serologic tests for syphilis. There was a disturbing lack of reproducibility in test results on repeat specimens of the same person and also variability in results when different types of antigen were used.

Male Versus Female: According to Rice,[86] a simple dilute-antigen modification of the standard Harrison-Wyler-Wassermann technique is of great value in distinguishing nonsyphilitic, or biologic, from syphilitic positive reactions. Both the sensitivity and the specificity of the test are increased. It is concluded that some dilute-antigen modification should be employed by all users of the Harrison-Wyler method. In a series of 15,385 tests a total of 290 such reactions occurred. Of these, 239 (82%) were detected as biologic reactions by this technique. Considerable differences were seen between females and males and between clinic and hospital cases. The percentage of biologic reactions was higher in pregnant women than in nonpregnant hospitalized patients. No other common cause for these reactions was found.

Pinta: The Universal serologic reaction devised by Kahn was studied in Mexican patients with pinta by Kahn and Villegas.[87] The serologic pattern was identical to that found in syphilis and similar to that in yaws.

Malaria: In a study of serologic response to experimental inoculation with Plasmodium vivax malaria in human volunteers, Olansky, Harris, and Hill [88] performed five reagin tests and the treponemal immobilization test on 130 persons. Blood was drawn before inoculation and approximately 10 days after the maximum parasite counts in the blood were obtained. Tests for reagin were positive or doubtful in 3.8% to 82.3% of the postinoculation specimens. Serologic tests employing cardiolipin showed a markedly lower incidence of positive reactions than did those employing lipoidal antigens. The treponemal immobilization test was positive in 19.4% of the preinoculation specimens and in only 9.7% of the postinoculation specimens. In only two cases was the test reactive in the same patients both before and after inoculation. Inasmuch as all these volunteers were screened for absence of syphilitic infection, it would appear that some technical difficulties in the laboratory interfered with accurate performance of the TPI test.

Leprosy: Portnoy, Galvez, and Cutler [89] subjected 51 leprosy patients in Guatemala to a battery of five serologic tests for syphilis. They found a much higher percentage of biologic false-positive STS in patients with "cutaneous" form of leprosy than in those with the "neural" or "podalic" forms. Varying with the sensitivity of the test, positive or doubtful reports were found in 35 to 90% of patients with the "cutaneous" form of leprosy and in 22 to 59% of all the leprous patients. To compare the tendency of various antigens to give false-positive reactions, Kvittingen and his colleagues [90] examined 955 samples of serum from lepers (821 in the initial tests and 134 in the follow-up tests) at the WHO Venereal Disease Laboratory, Simla, India. Findings showed that the tendency of lepers to have false-positive reactions is not lessened by the use of cardiolipin antigens instead of crude antigens. The Meinicke slide test was performed on all samples, the VDRL test on 952, and the Kahn test on 623. The Meinicke slide test gave positive reactions less frequently than did either the VDRL test with cardiolipin antigens or the Kahn test with crude antigens. Kvittingen [91] points out that, in testing serums from lepers, certain observations concerning the serum reagins which gave false-positive reactions were made by the WHO Venereal Disease Demonstration Team at Simla, India. Floccules of the serums which gave false-positive reactions in the VDRL and Kahn tests were extremely coarse in size and very compact. Serum reagins which reacted only in the VDRL or the Kahn

test tended to decrease in strength when the samples were kept at room temperature over a period of time and were destroyed when the serums were heated for five minutes at 65 C. The Meinicke test rarely gave false-positive reactions. It was suggested that the cholesterol in the VDRL and Kahn tests might be responsible for the false-positive reactions.

Lupus Erythematosus: Biologic false-positive serologic tests for syphilis have frequently been observed in patients with all types of lupus erythematosus. The time relationship between the development of these serologic alterations and the onset of clinical manifestations of lupus erythematosus is unknown. Haserick and Long [92] have been unable to find reports of cases in which false-positive tests for syphilis were observed prior to the clinical manifestations of lupus erythematosus. In their communication they report five cases in which false-positive serologic tests for syphilis were observed before the onset of clinical manifestations of systemic lupus erythematosus. In a series of 29 patients with systemic lupus erythematosus observed at the Cleveland Clinic during the past two years, seven have had positive serologic reaction to the test for syphilis. In one, a history of infectious syphilitic lesions was obtained. Another, a 13-year-old girl, was found to have positive serologic reactions to the tests for syphilis only after the onset of classic accute disseminated lupus erythematosus. In the remaining cases, positive serologic reactions to the tests for syphilis occurred one to seven years before the first symptoms of systemic lupus erythematosus. These data suggest that patients with positive serologic reactions to the tests for syphilis who have atypical rheumatoid arthritis, rheumatic fever, or glomerulonephritis may actually have latent systemic lupus erythematosus. The plasma L.E. test is recommended as a diagnostic procedure in such cases. The authors suggest the existence of a predisposition for lupus erythematosus. Shearn and Pirofsky [93] analyzed 34 cases of disseminated lupus erythematosus from the standpoint of clinical and laboratory features and response to therapy. Positive serologic reactions for syphilis were encountered in 19% of the cases, as compared with 43% reported in a previous study.

Liver Disease: Geier and Doepfmer,[94] on the basis of a large amount of material, were unable to confirm the idea that there is a relationship between icterus (liver disease) and nonspecific positive seroreactions.

### TREPONEMAL IMMOBILIZATION TEST

In 1952 interest in the Nelson and Mayer procedure has become intense. A number of general presentations have appeared.† Chorpenning [95] has reviewed the status of the treponemal immobilization test on the basis of his own experience and the literature. This leads him to conclude that the procedure provides a highly specific method of establishing, or eliminating, a diagnosis of syphilis in patients suspected of having infection on the basis of a positive STS. Nelson ‡ describes his work in experimental syphilis since 1947. One section is devoted to his experimental work which led to the discovery of treponemal immobilizing antibody and to the various ways in which the resultant test (TPI) has been

† References 95-100.

‡ References 96 and 97.

applied to clinical patients and to experimental animals. Much of this material has already been published. However, certain new applications are described, e. g,. a study of 75 patients with leprosy, of whom 57 were found positive with standard reagin tests employing cardiolipin antigen and only 13 were found reactive with the TPI test.

A second section concerns original work done at the Naval Medical Research Institute, wherein treatment of rabbits by x-irradiation (600 r two days prior to infection) was found to inhibit the formation of immobilizing antibody for several days, as compared with nonirradiated controls. It is suggested that this technique is of practical import in obtaining treponemal antigen for the TPI test, since small amounts of antibody from the rabbit host may contaminate the antigen and cause false doubtful or false-positive TPI tests.

As to the potentially important adhesion-disappearance phenomenon, it seems best to describe this in the author's own words, quoted from Paper C:

> In November of 1950, we first began experiments designed to demonstrate in vitro phagocytosis of T. pallidum. This work was begun for two main reasons: first, logical analysis of immunity in syphilis impressed me, along with many previous investigators, that phagocytosis ought to occur, but probably had never been proved due to some technical difficulty; second, an attack on this problem seemed feasible since techniques developed during the work on immobilizing antibody yielded tissue-free suspensions of treponemes which were ideally suited for phagocytosis experiments. Our first experiments were performed with techniques similar to those of Maaloe.
>
> In brief, the technique consisted of mixing tissue-free suspensions of treponemes, either living or heat-killed, with syphilitic serum. The mixture was then exposed to heparinized whole blood, freshly collected from a normal individual. After incubation at 37°C., there was a striking disappearance of the treponemes from the mixtures when examined directly, or from the supernatant fluid obtained after the mixtures were gently centrifuged to remove the blood cells. No such disappearance occurred with treponemal suspensions mixed with nonsyphilitic serum and then exposed to whole blood.
>
> Preliminary studies established clearly that specific antibody was essential in the "disappearance-phenomenon." By means of absorption techniques it was possible to prove that the antibody responsible was distinct and separate from Wassermann reagin. As yet, it has not been possible to determine the relationship of this antibody to, or its possible identity with, treponemal immobilizing antibody.
>
> The preliminary investigations also clearly establish that a heat labile component of normal serum, presumably complement, was essential for the reaction to occur.
>
> Early work suggested that this phenomenon was due to phagocytosis of the sensitized organisms by leucocytes, in the presence of complement, in the classically described sequence of events. However, the sequence of events and the main factors involved in this reaction, have been studied and the conclusions shown in Figure I have been obtained. It appears likely that these data represent the key to an understanding of this complex, but nonetheless most interesting, immunological phenomenon.
>
> 1. The results of this investigation to the present time indicate that the immunological phenomenon involving the 'disappearance' of sensitized T. pallidum from suspensions containing blood cells, and finally white blood cells. It is suggested that the last step is phagocytosis.
>
> 2. A definite immunological role of erythrocytes in this reaction has been established. To my knowledge, no previous evidence has been described of red blood cell reactivity in such a specific immunologic phenomenon. While it is well known that certain viruses and many other materials have been demonstrated to be absorbed onto the surface of erythrocytes, it should be reemphasized that non-sensitized T. pallida do NOT adhere to the red cell; and, further, that the adherence of sensitized T. pallida to the red cell appears to be specific, in that the sensitized treponeme will not adhere to other cells such as the white blood cells, platelets, and yeast cells.
>
> The actual mechanism of the action of the red cells is under investigation.

3. While it has been possible to utilize the occurrence of the adhesion-disappearance phenomenon in a preliminary evaluation of its use as a diagnostic procedure, the complexity of the four steps of the reaction suggest that considerable experience must first be obtained with the purely investigative aspects of the phenomenon before it can be used as clinical test.

*Theoretical Steps in the Reaction of Virulent T. Pallidum in Vitro with Antibody, Complement, and Normal Human Blood Cells*

| | |
|---|---|
| 1. TP +Ab—TP —Ab | Sensitization<br>a) Antibody is distinct from Wassermann Reagin |
| 2. TP —Ab +$C^1$—TP —Ab<br>$C^1$ | Complement Fixation<br>a) Active component is heat labile fraction of normal serum, presumably $C^1$ |
| 3. TP —Ab +RBC—TP —Ab —RBC<br>$C^1$ $C^1$ | Adhesion Phenomenon<br>a) Adhesion does not occur with platelets or with leucocytes<br>b) Adhesion does occur with lysed erythrocytes (ghost cells) |
| 4. TP —Ab —RBC +WBC—Total<br>$C^1$ Disappearance | Disappearance Phenomenon<br>a) Probably phagocytosis?<br>b) TP —Ab —WBC—Total Disappearance<br>$C^1$ |

(Ab = anitibody; $C^1$ = complement)

The following discussion is a portion of a review of this subject by one of us (Beerman, H.: The Treponemal Immobilization Test, *Am. J. M. Sc.* **226:** 425-441 [Oct.] 1953). Since the material is largely from the present review period, the data are presented nearly verbatim.

Several centers for the study of the treponemal immobilizing phenomenon have been established in France, particularly those of the Institut Alfred-Fournier and of the Hospital Saint-Lazare. The authors review their earlier publications on this subject, which confirm the fundamental observations of Nelson and Mayer. The present investigation of Levaditi, Vaisman, and Hamelin [99] describes further clinical and experimental studies, the former based on 1,300 additional TPI tests performed in the early part of 1952. These clinical observations confirm the value of TPI test for the recognition of biologic false-positive serologic tests and its diagnostic value in the occasional patient with late syphilis, seronegative with standard techniques. The authors have followed a small number of patients with early syphilis by both standard and TPI serologic tests and again confirm the fact that reagin disappears before the immobilizing antibody.

From the experimental point of view, the authors have examined the TPI test in several species of animals infected with syphilis (other than the rabbit). These include mice, rats, and hamsters. They have obtained variable results in mice and rats (number of animals not stated), but a small group of hamsters infected with syphilis all developed immobilizing antibody. The authors have further confirmed the fact that T. pallidum, immobilized by the antibody in question, loses virulence.

The next experiment deals with the inoculation of rabbits with T. pallidum (Nichol's strain) killed by heat, Formol, or ultraviolet irradiation. Such animals did not develop immobilizing antibody, nor were they immunized against infection with living organisms.

The behavior of immobilizing antibody has been studied following ultracentrifugation at high speed. Under these circumstances, reagin disappears from a seropositive serum, whereas, on the contrary, immobilizing antibody remains unchanged. Likewise, agglutinins against Salmonella typhosa (Eberthus typhosus) and antisheep hemolysin disappeared from serum under ultracentrifugation. On the basis of these experiments the authors conclude that the immobilizing antibody is lighter in molecular weight than the other antibodies mentioned.

Finally, the authors have studied the cross reactivity of immobilizing antibodies with T. pallidum with those produced by experimental infection with Borrelia duttonii and Borrelia (Spirochaeta) gallinarum. Each of these two latter infections produced specific immobilizing antibodies, which are not cross reactive with the treponemal immobilizing antibody.

The same authors [100] have treated a number of rabbits, experimentally infected with syphilis, by means of the intramuscular injection of bismuth and have studied the behavior of the TPI antibody before, during, and after this treatment and after challenge reinoculation. They conclude that bismuth cures experimental syphilis and that during the course of this cure the TPI test becomes negative. After reinoculation the animals failed to develop any evidence of testicular lesions but did again demonstrate virulence of the lymph nodes, and the TPI test again became positive.

A compilation of French experience indicates a generally favorable attitude toward the TPI test.§ Boudin and Blancher [113] use the test as a definitive means of diagnosis of neurosyphilis, since a negative result, in their opinion, means absence of neurosyphilis. Merklen and Berthaux [114] found agreement between the Nelson and Mayer technique and the Neurath test, a procedure rarely employed now. Rabut,‖ on the other hand, does not believe that so complicated, unreliable, and costly a test as the TPI test is necessary. In a well-documented, detailed, and critical response to a previous summary communication by Nelson,[117] Touraine [118] states that although there are decided advantages to be derived from the TPI test its wide adoption should be withheld until the various difficulties and uncertainties connected with it have been resolved. A somewhat similar doubtful view had previously been expressed by Barnett (Barnett, C. W.: The Treponemal Immobilization Test in the Diagnosis of Syphilis, *Stanford M. Bull.* **9:** 205-206 [Nov.] 1950), of the United States, who believes that it appears that the TPI test, because of technical difficulties, is not available for routine use and that it is doubtful if it ever will be feasible to utilize it on a very large scale. Although Thivolet [111] had a satisfactory experience with the procedure, he too believed that it was a laborious routine, with numerous pitfalls. Binazzi, of Italy,[34] made use of the procedure in a comparative study of syphilitic antibodies in blood, bone marrow, and blister fluid.

In Copenhagen, Reyn and Nielsen [103] determined the reagin contents and treponemal immobilizing antibody in 89 sera from 79 patients. Reagins were demonstrated by the following seroactions: Wassermann's complement-fixation test as modified by Mørch (WR-M); the same, using cardiolipin antigen (C-WR-M); Kahn's standard test (KR), and Meinicke's clarification test (MR). Immobilizing antibodies were demonstrated by Nelson's technique, which was carefully adhered to; most of the sera were evaluated qualitatively only. The material was

§ References 101-112.

‖ References 115 and 116.

divided into three clinical groups: (1) 25 sera from patients with syphilis; (2) 19 sera from clinically doubtful cases, and (3) 45 sera from patients in whom the possibility of syphilis could be excluded with almost complete certainty. In Group 1 the reagin and TPI results showed the highest conformity; in Group 2 and, especially, in Group 3 more discrepancies were found. In regard to sensitivity of the TPI test, no definite conclusions could be drawn on the basis of the limited number of sera examined in Group 1. The results confirmed previous investigations showing the high specificity of the TPI test. Durel and his group [119] made a survey of results obtained in the first 1,000 cases, representing a survey of 1,466 tests (many patients had repeated tests). Their results are as follows: (1) Untreated patients. The TPI test is of little value in the diagnosis of syphilis in contacts of cases of infectious florid syphilis, as the diagnosis can best be made by methods already available. In cases of latent infection of long duration, however, the TPI test may afford the only proof of infection. The TPI test is especially valuable for patients presenting lesions suspected of being syphilitic, particularly when these suggest late or congenital syphilis. When the STS is frankly positive or negative, similar results are usually obtained with the TPI test. It is most useful in interpreting intermediate results obtained with the STS and may detect biological false-positive reactions. (2) Treated patients. The TPI test sometimes gives help in the retrospective diagnosis of a patient incorrectly treated as syphilitic. It has great value in judging the part played by syphilis in patients known to have had the disease who present lesions which may be attributable to it. Theoretically, it may aid in discrimination between relapse and reinfection, provided that a series of tests have been carried out, a condition rarely fulfilled at present. It has raised doubts about the therapeutic provocation method, the results of which may only be due to biological false-positive reactions. (3) Relations to various forms of treatment. Penicillin therapy results in a better negative response with the TPI procedure than does the older arsenic and bismuth therapy; the sooner treatment is started the quicker the action on the TPI reaction. The TPI reaction affords a new possibility of establishing cure when it is negative on two occasions; this is open to question, as healing and antibody production are not definitely related. A TPI reaction that remains positive after treatment has no prognostic value. (4) Comparison with STS. Careful quantitive STS usually but not invariably agree with the TPI test results. Total positivity of the two types of test is more often seen (88.9%) than total negativity (71.4%). Possible causes of discrepancy are discussed. (5) The TPI test shows a few peculiarities in early syphilis: no elaboration of detectable antibodies; delay; "peak" phenomena. (6) The results of the TPI test on the cerebrospinal fluid in 58 cases are reported. No positive results are found which are not also positive with the serological tests. Frequent discrepancies are found with regard to the Wassermann reaction.

Miller and his co-workers [120] state that in their experience the treponemal immobilization test proved highly accurate in the diagnosis of human syphilis. Their report was based on 455 patients, composed of 123 with proved syphilis, 250 diagnosed as having latent syphilis, and 82 nonsyphilitics. The treponemal immobilization test was positive at the time it was made in all cases of proved congenital, central nervous system, cardiovascular, and early latent syphilis; the same was true of gummas. In the group of patients with primary and secondary syphilis, the interval from the time of diagnosis to the time of the treponemal

immobilization test varied from 0 to 48 years. Of the 30 patients diagnosed as having primary syphilis, 4 had negative treponemal immobilization tests; of 39 with diagnoses of secondary syphilis, 2 had negative treponemal immobilization tests. The negative results occurred in patients who had had adequate treatment in the early stages. The test also yielded negative results in 9 instances, or 5%, of the 213 patients thought to have late latent syphilis. Of these nine patients with negative reactions to the treponemal immobilization test, three had been treated for syphilis more than 30 years previously and their reactions to the serologic tests for syphilis were still fluctuating. Two patients had been treated for syphilis more than 10 years previously, and their reactions to the serologic test for syphilis were positive. The remaining four patients had had a diagnosis of syphilis for less than 10 years. In two of these, the reactions to the serologic tests for syphilis were becoming negative at the time the treponemal immobilization test was performed. The condition of the third patient, with a low titer as determined by the serologic test for syphilis, was not influenced by treatment. The fourth patient had a very high titer, not influenced by large amounts of penicillin. Every one of the 82 non-syphilitics had a negative reaction to the treponemal immobilization test. These tests were made on patients with a wide variety of diseases and would offer opportunity for a false-positive reaction. Miller and his group found none. They did encounter a number of examples of unexpected positive reactions to the treponemal immobilization test; when the patients were confronted with the evidence, an admission of a previous syphilitic infection was obtained in every case.

Miller and his co-workers[121] have also reported their findings on the use of the treponemal immobilization test in 170 patients studied subsequent to their previous report on 455 patients. Of 99 patients diagnosed as having probable biologic false-positive reactions, the treponemal immobilization test was positive for 3 who had had yaws and was negative for the remaining 96. The serologic test for syphilis was positive for all these patients. In another group, with a questionable diagnosis of syphilis, the treponemal immobilization test was negative in almost one-half. The authors conclude that the treponemal immobilization test is an extremely reliable test in the diagnosis of human syphilis. According to Moore and Mohr,[88] studies at Johns Hopkins University and elsewhere have provided much more information about the treponemal immobilizing antibody, as follows: 1. It does not occur in the serum of normal persons or of those suffering from nontreponemal diseases; 2. It does occur uniformly in syphilis and the closely related treponematoses, yaws, pinta, and bejel, but not in other spirochetal diseases, such as leptospirosis, relapsing fever, ratbite fever, or Vincent's infections; 3. In untreated syphilitic infections its rate of appearance in the serum approximately parallels that of reagin; it is first detectable when the primary lesion is from 5 to 15 days old and rapidly increases in titer for the first few weeks, reaching a plateau at about the second or third month of infection. However, in syphilitic rabbits it does not decline or disappear from the serum following the spontaneous healing of the chancre, as does reagin, and it is probable (though not yet finally verified) that in man it does not spontaneously decrease in titer with the passage of years. In patients with untreated syphilis, during and after the secondary stage, it is almost certainly always present for the duration of the patient's life, even though reagin may have spontaneously disappeared, and the treponemal immo-

bilizing test is therefore a useful diagnostic tool in reagin-free patients, i. e., those with negative standard serologic test, with lesions possibly due to syphilis, such as in the differentiation between rheumatic and syphilitic aortic insufficiency. 4. In treated early (primary, secondary, or early latent) syphilis, treponemal immobilizing antibody disappears from the blood, as does reagin, but at a slower rate and not necessarily in a parallel manner. Thus, patients treated for early syphilis are usually found, years later, to be seronegative with both tests, though sometimes their reactions are positive for treponemal immobilizing antibody and negative for reagin. 5. In treated late syphilis, i. e., of several years' duration, on the contrary, treponemal immobilizing antibody usually does not disappear from the serum, though reagin may do so; such patients examined from 1 to 35 years after clinically successful treatment of late syphilis, of whatever type, are 95 to 98% positive-reacting to treponemal immobilizing antibody.

These and other data permit the tentative conclusion that the treponemal immobilization test detects an antibody specific for syphilis and the related treponematoses and that it may be expected, in a modified form, eventually to replace "standard" serologic tests that depend on lipoid antigens for detection of the nonspecific reagin. Unfortunately, this goal is not yet in sight, though efforts at simplification of the test are in progress and are promising. The treponemal immobilizing test is expensive, and since it is not yet possible to cultivate virulent T. pallidum in vitro, its performance depends on the maintenance of a large rabbit colony as a source of supply of living treponemes. It requires the use of sterile serum (or spinal fluid). It is time-consuming, complicated, and subject to numerous technical pitfalls. These difficulties have so far limited its use, largely on an experimental basis, to six or eight laboratories in this country, and it is not yet ready for adoption by the thousands of existing serologic laboratories.

Nelson [122] has recently advocated that for the United States Navy the treponemal immobilization test, or some future modification of it, serve as a final criterion for diagnosis of patients with "suspected" latent syphilis on the basis of a positive standard reagin test. In patients with positive reagin test, shown to be falsely positive by virtue of a negative TPI test, an extensive effort should be made to determine by medical examination and other laboratory investigation the factors responsible for the false-positive reagin test.

*Treponemal Immobilization Test and Biologically False-Positive Serologic Reactions.*—For a long time, it has been known that the standard serologic procedures employed in the diagnosis of syphilis produce false-positive reactions due to a variety of diseases and conditions. The available literature on this subject has been analyzed by a number of students. To the present, all attempts to devise a specific serologic method for the diagnosis of syphilis have failed. Accordingly, the indication that the Nelson-Mayer procedure was at last the possible answer to the problem of biologic false-positive serologic reactions was hailed with intense interest. Levaditi and his group [99] believed that the test was of exceptional importance in ferreting out false-positive reactions to the lipoid tests. Gaté, Sohier, Thivolet, Saucaz-Larame, and Rolland,[106] from a study of 47 subjects, believe that a positive TPI result means syphilis. Olansky and his colleagues,[88] in the United States Public Health Service, made a preliminary report of apparent biological false-positive reactions in four serological tests for syphilis and the treponemal

immobilization test. They thought that the TPI test, as performed in their study, showed poor reproducibility but no trend toward an increased number of false reactions in the presence of malaria.

The outstanding presentation indicating the value of the TPI test as a means of solving the biologic-false-positive-serologic-reaction problem is that of Moore and Mohr.[83] According to these authorities,

> From the earliest development of the treponemal immobilizing test, it was obvious that its most practical and clinically important use might lie in the differentiation of the positive standard serologic test due on the one hand to syphilis and on the other hand to the biologically false positive phenomenon. This is in fact the case. Nelson and his associates have demonstrated that the treponemal immobilizing test was negative in 12 acute biologically false positive reactors, in whom the false positive standard test was due to the following causes: primary atypical pneumonia in 6, infectious mononucleosis in 1, malaria in 1, chickenpox in 2, and measles in 2.
>
> We, on the other hand, have applied the test to the recognition of the much more frequent, difficult, and complicated problem of the chronic biologically false positive reactor. The validity of the test, under these circumstances, depends on the observation that in treated late syphilis, the treponemal immobilizing test remains positive, presumably for the duration of the patient's life, and in spite of the type or amount of previous treatment.
>
> Our clinical material consists so far of 300 patients known to be seropositive with standard techniques for six months or longer (in some cases, as long as 10 to 15 years), and in whom the diagnosis lay between latent syphilis (no manifestations except the positive serologic test for syphilis) and the chronic biologically false positive phenomenon. Before the performance of the treponemal immobilizing test, our patients were assigned to one or other of these categories on the basis of the presence of the collateral evidence.
>
> The results of the treponemal immobilizing test in these two groups and in a group of 256 patients with clinically verified late syphilis, and the comparison of these results with clinical judgment are shown. In the category of "syphilis, late, treated" the diagnosis in all cases depended on the presence of clinically recognized lesions of the infection. In those classified as "probable latent syphilis" or "probable biologically false positive reactors," the clinical diagnosis depended on a verified positive standard serologic test for syphilis, plus, in each case, all or most of the collateral studies.
>
> From these data, it is suggested that there is a margin of error in both directions, which is probably of clinical judgment rather than of the treponemal immobilizing test, i. e., about 15% of patients in whom we had diagnosed latent syphilis were actually biologically false positive reactors; and 16% of those whom we had thought to be nonsyphilitic actually had syphilis. Nevertheless, the agreement between clinical diagnosis and the results of the treponemal immobilizing test is remarkably close.
>
> Other than our own study and some as yet unpublished observations of Nelson in the United States Navy, nothing is known so far of the incidence of chronic biologically false positive reactors. This information will not be forthcoming until larger scale serologic surveys have been undertaken in which all seropositive reactors with standard tests are checked by the treponemal immobilizing test. A guess may be made, however, that the phenomenon is frequent, since in our own practice, 43% of patients in whom in earlier years latent syphilis would have been diagnosed have now been identified as biologically false positive reactors.
>
> Use of the treponemal immobilizing test permits, for the first time, a definite answer to the question, "Does this patient have syphilis?" When this question is answered in the negative, however, it is at once replaced by another and perhaps even more serious question: "What is the cause of the chronic biologically false positive phenomenon?" The answer to this latter question is not available from the existing literature. Surveys of the incidence of presumed biologically false positive reactions in this or that population group or in this or that nonsyphilitic morbid process are not valid, because positive standard tests with lipoid antigens have in no instance been checked by the treponemal immobilizing technique (except in the case of leprosy).
>
> The etiologic background of the chronic biologically false positive phenomenon is under study in this clinic, by means of a long term clinical follow-up of such patients. Only preliminary results are so far available, but these indicate that the biologically false positive reaction is not

innocuous, to be dismissed lightly, but is often, perhaps usually, a manifestation of serious underlying disease. Outstanding among the conditions so far identified in a substantial proportion of biologically false positive reactors are the collagen diseases such as disseminated lupus erythematosus, periarteritis nodosa, rheumatoid arthritis, and rheumatic fever, and sarcoid. Further details of these studies will appear later.

*The Treponema Pallidum Immobilization Test in the Study of Immunity in Syphilis.*—Although a state of true resistance to reinoculation arises in syphilitic infection,¶ the mechanism of this immunity is not clear. Attempts to produce active immunity in experimental animals by the inoculation of killed T. pallidum have been either unsuccessful or unconfirmed. Since the introduction of specific circulating treponemal antibodies in the serum of syphilitic patients and rabbits by Nelson and Mayer, interest has been centered around the significance of this antibody in terms of immunity. In rabbits, it has been demonstrated that during the time when active immunity and immobilizing antibody are both increasing with the duration of the infection, the degree of resistance is slightly paralleled by the height of the antibody titer. But other investigators have demonstrated that there is no necessary dependence between these two factors. In experiments with rabbits with latent syphilis, which had been infected for similar lengths of time and then treated, in 1949, they had already found that the degree of resistance could not be correlated with the TPI titer to challenge or with the extent of an amnestic rise which followed the challenge. In addition, McLeod and Magnuson[125] noted an immunological relationship between syphilis and yaws spirochetes through cross immobilization tests. Thus rabbits with experimental yaws developed high levels of no resistance to challenge with small numbers of this organism. The earlier report by McLeod,[126] indicating that immobilizing antibodies were produced in mice by the injection of killed Nichol's strain T. pallidum, has provided a useful method for study of the mechanisms of immunity in syphilis. McLeod and Magnuson[125] have reported, in a more recent contribution, the immunologic response of both rabbits and mice to inoculations of killed organisms. Such injections provoked both a rise in the TPI titer of treated rabbits and the development of TPI antibodies in normal rabbits, and these antibodies were present in both rabbits and mice which were not immune to inoculation with universal doses of the homologous strain.

Immobilization reactions have been variously reported in a number of animals infected with other species of spiral organisms. Gelperin[127] noted that in Nelson's hand serum from Group II and III rabbits (Group II was injected intravenously and intraperitoneally with a saline suspension of Reiter's spirochetes; Group III rabbits received subcutaneous injections of the vaccine in adjuvants) failed to yield evidence of immobilization antibodies to T. pallidum, in contradistinction to partial protection observed under these circumstances. This discrepancy may have been the result of differences in sensitivity of the two tests and/or the cross-reactivity of a virulent strain and a virulent variant. Levaditi and his school have approached the problem of late syphilis by a study[128] of the immobilizing antibodies produced by several spiral organisms. The occurrence of spirillicidal spirillolytic antibodies and opsonins in the serum of animals or humans infested by recurrent spirochetes (Borrelia duttoni) was demonstrated years ago. Levaditi, Vaisman, and Hamelin[129] have demonstrated by the Nelson-Mayer technique

¶ References 123 and 124.

specific immobilisins capable of acting against Bor. duttoni in the serum of the mouse, rat, guinea pig, and a patient with general paralysis during the course of the involution of the spirillosis. Levaditi, Vaisman, and Hamelin [130] found that immobilisin against Bor. duttoni acts on Spirochaeta hispanica and that the antitreponemic immobilisins are without effect on Bor. duttoni. Levaditi, Vaisman, and Hamelin [129] have also employed the Nelson-Mayer test for identification of strains of T. pallidum. Levaditi's group # has been unable to induce immunity in rabbits by inoculation of spirochetes devitalized by exposure to ultraviolet irradiation. Nor did these inoculated animals develop immobilizing antibodies. Treatment of syphilitic rabbits with bismuth caused the previously positive immobilization reaction to become negative, leaving the rabbits susceptible to a new infection. Levaditi, Vaisman, and Hamelin considered this to indicate that the animal is as receptive to infection as is a new animal.

Some consideration has been given to the question as to whether the immobilizing antibodies affect the virulence of T. pallidum. Levaditi, Vaisman, and Hamelin,[133] employing rats, were able to confirm the previous results, found with rabbits, that immobilization of T. pallidum implies loss of virulence of the organisms.

Vaisman and Hamelin * were able to separate from syphilitic serum the "reagin" of immobilization by ultracentrifugation at great speed. The differentiation between the two principles shown by chemical and biological means is further confirmed by a biophysical technique. They also employed this technique to separate antityphic agglutinins and antisheep hemolysins from the immobilization factor, thus distinguishing the antitreponemic immobilisins from agglutinins and hemolysins. Jordan [136] has also demonstrated the separate identities of the Donath-Landsteiner hemolysin (paroxysmal cold hemoglobinuria) and treponemal immobilizing antibody.

*Technical Shortcomings of the Treponema Pallidum Immobilization Test.*— From the presently available information there is ample evidence that the Nelson and Mayer treponemal immobilization test has great possibilities in many directions in syphilology, but there are still many technical difficulties connected with it. These deficiencies may prevent wide adoption of the procedure. Although certain technical refinements have already been made or suggested,† the greatest problem is providing for adequate supply of motile, virulent treponemes. To this end there have been a number of suggestions, chiefly in the direction of storage of the organisms at low temperatures ‡ and prolonging their survival time by exposure to 5% carbon dioxide and cold temperatures.[139] The immobilization test can be performed with organisms from frozen testis [141] with results comparable to those obtained with treponemes from fresh syphilomas. The use of cortisone as well as reticuloendothelial blotting methods [142] in experimental syphilis may be adopted to this problem, since lesions of infected animals treated with this preparation or methods (roentgen rays or methyl-*bis* or *tris* [β-chloroethyl] amine hydrochloride [nitrogen mustard]) exhibit actively motile T. pallidum and other

# References 131 and 132.

* References 134 and 135.

† References 119 and 137.

‡ References 138-141.

spirochetes in considerably larger numbers than are found in control lesions.[143] § In spite of the technical shortcomings of the test, continued interest in it in the United States is indicated by the fact that it is still under investigation in at least seven laboratories.[144]

Because the recent communication of Magnuson [150] states the present status of the TPI test so well, it is quoted here:

> The treponemal immobilization test can only measure the presence of treponemal immobilizing antibodies. The clinical significance of the presence or absence of such antibodies must be assessed in relation to collateral evidence obtained from the patient's history, physical findings, and other serologic tests. It must also be interpreted in the light of general as well as specific immunologic knowledge. Present evidence indicates that treponemal immobilizing antibodies develop only in response to either treponemal infection or injection of killed treponemes. Thus, a repeated positive treponemal immobilization test is more specific evidence of a treponemal infection than a repeated standard serologic test with lipid antigens. The significance of a negative result in the treponemal immobilization test is less certain. In the untreated syphilitic patient who has gone beyond the secondary stage, a negative result is probably rare. The treated patient presents a more complicated problem, since treponemal immobilizing antibodies are known to disappear in a large proportion of patients treated early in the course of the disease. Thus, for the patient described in the query, the unequivocal statement, "The question of whether the patient described ever had syphilis can be answered by means of a treponemal immobilization test," is not in accord with known facts. If the test result is positive, the patient most probably had a treponemal infection; but, if the result is negative he may or may not have had syphilis.
>
> It also seems advisable to emphasize the restrictions in the interpretation of statements such as "the incidence of such biological false positive tests is probably about 30 to 40% of all positive reactors routinely discovered in certain population groups." There is an increasing tendency among physicians to consider as biologically falsely positive all positive serologic test results occurring in their practice. The limitations of present observations might be better expressed as follows: In patients with repeated positive standard serologic test results in whom there is no history or clinical evidence of syphilis and in whom the results of spinal fluid examination are

§ Increasing sodium thioglycollate in the basal medium and the use of high concentrations of guinea pig complement [145] have improved the performance of the procedure in respect to good survival controls; negative findings with known normal, nonsyphilitic, serums; a high level of sensitivity, and a few inconclusive findings. Saurino [146] also reduced the ambiguous reactions, by the use of a modified medium which contained ox ultrafiltrate for enrichment. Durel and his co-workers [147] described a grinder with interchangeable tubes of small capacity for obtaining treponemes for inoculation of new animals.

During investigations on the use of x-irradiation as a method to inhibit antibody formation in rabbits infected with T. pallidum (Nelson, United States Naval Research Institute), it was observed that organisms from irradiated animals did not undergo spontaneous agglutination in vitro, as did treponemes from nonirradiated animals, presumably because of specific antibody contributed by the rabbit host. Although specific agglutination of treponemes has been repeatedly described since the extensive work of Touraine, in 1911, the fact that many batches of treponemes from rabbit lesions have shown agglutination with normal serum or even with isotonic saline solution has prevented its development into a practical laboratory procedure. Cain [148] utilized treponemes from irradiated rabbits to assay 122 human sera which had been previously tested with the treponemal immobilization test. Agglutination in four to six hours at 37 C. was observed, with only one immobilization-negative serum. All immobilization-positive sera gave marked agglutination. Since heat-killed treponemes may be used for these experiments and since the suspensions of treponemes appear to be stable on storage at 2 to 4 C. (64 days minimum), the advantage of this technique as another serodiagnostic method in syphilis is suggested. The use of organisms from rabbits in which antibody in the host is inhibited by x-irradiation (or other techniques) is a significant advance in preparing suspensions which are free of the troublesome tendency to undergo spontaneous agglutination.

negative, a varying number will prove to have negative results in the treponemal immobilization test. Among such patients studied in our laboratory, the proportion showing positive treponemal immobilization tests has varied from 35 to 97%, depending on the racial, economic, and geographical origin of the group.

### CEREBROSPINAL FLUID

Several problems regarding the cerebrospinal fluid have again received consideration this year. Treatment of postspinal headache, however, is the chief subject of discussion. Nielsen,[151] whose Chief, Esbern Lornholt, had previously made a similar study, in 1936, found on the basis of his analysis of the findings of 428 patients followed through the Syphilitic Registration Office of the State Serum Institute, in Copenhagen, that a negative spinal fluid at the first examination in latent syphilis guarantees a good prognosis with regard to neurosyphilis. If the spinal fluid is positive at the first examination in latency, the degree of the changes observed gives important information as to the prognosis in the direction of therapy. This is an important study. The good prognostic importance of a negative spinal fluid examination in latency is generally accepted, but we have seen a number of exceptions, in which the patients subsequently developed positive reactions, so that we continue to accept this thesis with reservation. For example, Livingood and Beerman,[152] in 1941, reported the course of syphilis in two brothers, both of whom originally had negative spinal fluid findings but subsequently developed similar positive results in the spinal fluid. Courtin [153] points out that while lumbar puncture in the hands of the expert is a relatively simple procedure there are some hazards which must be taken into account. These include those occurring purely as a result of mechanical trauma arising from the insertion of the lumbar puncture needle, those arising from infection, and the actual complications of having introduced a needle within the subarachnoid space. Postpuncture headache is probably the most frequent complication, and all cases do not respond to the same therapy. Herniation of the medulla into the foramen magnum is the most dramatic hazard of lumbar puncture. It is the result of hypotension of cerebrospinal fluid within the spinal portion of the subarachnoid space. As a prophylaxis lumbar puncture should not be performed on patients who have signs of increased intracranial pressure.

*Treatment of Postspinal Headache.*—Deutsch,[154] in a report on 15 patients, has suggested a promising new therapy for postspinal headache. This involves physiological replacement of fluid at the other end of the cerebrospinal canal. The procedure consists of the intravenous injection of a solution of 5% ethyl alcohol in 5% dextrose in 1 liter of distilled water. The hope of the treatment is to dilate the vessels of the choroid plexus by the alcohol, to metabolize the dextrose rapidly, and to utilize the water for the formation of cerebrospinal fluid. Crosby [155] has suggested the use of $\beta$-pyridyl-carbinol tartrate (Roniacol tartrate) for the long-term headache following pneumoencephalography, and it is believed that this preparation may relieve the low-tension headache resulting from diagnostic lumbar puncture. Pfeffer [156] reports good results from treating postspinal puncture headaches with desoxycorticosterone acetate by mouth.

*VDRL, Kahn, and Kolmer Tests for Syphilis.*—Olansky and his co-workers [157] present and discuss the results obtained with the VDRL, Kahn, and Kolmer tests for syphilis, plus the status of cell counts and total protein determinations, on 5,539 spinal fluids drawn from patients in the treatment center at Alto, Ga. For

each 11 admissions to the Alto treatment center, an average of one spinal fluid (9.1%) gave positive or doubtful reactions in one or more of the three tests for syphilis used in this study during a six-month period. Results obtained with the VDRL and Kolmer tests were in closer agreement than were those of the VDRL-Kahn or Kahn-Kolmer test combinations. In 132 spinal fluids in which the results of the VDRL, Kahn, and Kolmer tests were not in agreement, slightly better correlation was obtained between the reactive VDRL tests and increased cell counts and/or total protein findings than existed between these two findings and the reactivity of the Kahn or Kolmer tests. Cannefax and Beyer [158] report on over 2,000 comparative qualitative tests on spinal fluids in three laboratories, utilizing the Kolmer-complement-fixation and the VDRL-flocculation tests. The results indicate that these tests present similar efficiencies in detecting reagin in spinal fluid. In a comparison of quantitative tests in the spinal fluid in 146 patients, the VDRL test appeared to be somewhat more sensitive. They conclude

> It appears that the VDRL flocculation spinal fluid test may replace the time-honored Kolmer complement-fixation test without a loss of testing efficiency and with a gain in economy of testing and rapidity of reporting.

*Effect of Procaine Hydrochloride (Novocain) on the Colloidal Gold Test in Cerebrospinal Fluid.*—Kercher found that the presence of minute quantities of procaine alters the colloidal gold test of cerebrospinal fluid. The reaction may simulate characteristic abnormal curves. The influence may be recognized by the color change that starts immediately upon addition of the gold sol and progresses to its end-point without visible change in the turbidity of the solution. Studies with the stabilized colloidal gold solution of Lange and Harris indicated a similar sensitivity.

## CLINICAL MANIFESTATIONS

The clinical manifestations of syphilis continue to excite the interest of the syphilologist. One would imagine that a disease of such antiquity as syphilis would be well known. The transmission of early syphilis by "natural" as well as unnatural means is the most noteworthy problem discussed. Epstein's analysis of the occupational hazard of syphilis to physicians should make every physician pay at least enough attention to this disease to keep himself from trouble. There is still need for a good and definitive study of latent syphilis. The lack of really new information on the clinical aspects of cardiovascular syphilis is compensated for by the great advances in therapy of this phase of syphilis. Knowledge of neurosyphilis and prenatal and congenital syphilis is reasonably stabilized, but wider study of the ocular manifestations of syphilis may yield fruitful returns in the near future.

In connection with the general discussion of the clinical manifestations of syphilis, Rein and Kostant,[160] in a provocative and interesting article, have recorded their opinions on a number of special problems in the handling of syphilitic patients. They emphasized that the contact of a person with infectious syphilis, treated prophylactically without clinical or laboratory evidence of the disease, should be followed with clinical, serological, and spinal fluid examinations in the same way as are patients diagnosed as having syphilis. Similarly, a pregnant woman who presents a positive reaction to the tests for syphilis, but for whom it cannot be determined definitely whether syphilis or a biologic false-positive reaction is responsible for the positive result, should be treated to prevent possible infection of the baby. After delivery, both the mother and the baby must be followed ade-

quately. These authors emphasize the frequency of positive serologic tests in nonsyphilitic infants under three months of age born of mothers with positive STS. The diagnosis of syphilis in new-born infants is warranted only if there is darkfield demonstration of T. pallidum from the scrapings of the umbilical cord, definite clinical or radiologic evidence of an active syphilitic process, or failure of reduction or progressive increase in serologic titer over a period of weeks or months, usually associated with early syphilis in the mother late in pregnancy with inadequate or no treatment. When the differential diagnosis lies between biologic false-positive reaction and latent syphilis, exhaustive studies, including the treponemal immobilization test, should be carried out in an effort to make a definitive diagnosis. When such an adequate work-up is not feasible, therapy probably should be administered. Once this is done, the patient should be considered as a person with probable latent syphilis and followed in the same manner as is a person with proved syphilis. In discussing indications for retreatment of syphilitic patients, the authors advise that, in patients treated initially for early syphilis, every effort should be made to differentiate between asymptomatic reinfection and serorelapse. They recommend retreatment with penicillin alone and epidemiologic study of these patients at the time of retreatment. Following treatment of persons with late syphilis, retreatment should be instituted only if there is clear-cut evidence of clinical or serologic relapse. In regard to neurosyphilis, the authors advise that retreatment should be instituted only when there is evidence of activation in the spinal fluid findings, i. e., an increased cell count and protein level. Larger doses of penicillin should be administered over a longer period of time, and fever therapy should be employed when indicated. Concerning syphilis in pregnancy, the authors advise against retreatment simply because of a persistently positive STS. Retreatment should be instituted when the patient presents clinical evidence of relapse or reinfection, a rise in serologic titer which is maintained or increases on subsequent examinations, or persistently high-titer STS during the last trimester of pregnancy. This paper covers well a number of current problems. However, the increasingly important problem of differentiation in treated patients between seroresistance of late syphilis and serorelapse of early syphilis [161] is completely neglected.

## EARLY SYPHILIS

The essential facts about early syphilis have been summarized by Catinella.[162]

*Transmission of Syphilis.*—Risk of Syphilis Infection by Sexual Intercourse with Syphilitic Partner: Schäffer and Sylvest [163] found that of 50 persons who had had sexual intercourse with a syphilitic partner within the incubation period and/or in the first and/or the second phase of the disease about one-half became infected with syphilis. The risk of infection was smaller, but still considerable, when coitus had taken place exclusively within the incubation period (between one-fourth and one-third infected) than when the partner had syphilitic cutaneous or mucosal lesions (about two-thirds infected). Grünberg and Theune [164] studied 123 cases of early syphilis to determine the rate of transmission to the marital partner. In primary syphilis less than half and in secondary syphilis about two-thirds of the partners are infected.

Syphilis and Transfusion: Transfusion syphilis is rarely heard of now, because of more sensitive tests for detection of syphilis in prospective donors and the widespread use of the blood bank.[165]

Occupational Hazard to Physicians: Epstein's [166] recent survey of syphilis as an occupational hazard to physicians was the subject of an excellent editorial in *The Journal of the American Medical Association.*[167] A total of 51 cases of extragenital chancres in physicians were reported by 32 of 125 dermatologists who answered questionnaires. In 35 instances the syphilitic lesions occurred on the fingers, in 6 instances in the nasal cavity, in 1 on an eyelid, and in 1 on an arm. Six cases of accidentally acquired syphilis were observed in interns, residents, and medical students. Otoloryngologists were more frequently affected than any other well-defined group, and lesions developed in six of them; five cases occurred in general practitioners, and two were detected in pathologists. Routine clinical examination of patients produced infection in seven physicians, while in five physicians syphilis was acquired during obstetric procedures or during pelvic examinations of patients. Three cases were attributed to tonsillectomy, three cases to wounds produced by needle puncture, and two cases to exposure during surgical performance. Epstein's report of 51 cases of extragenital primary syphilitic lesions in physicians indicates that syphilis constitutes a definite occupational hazard in the medical world. Along the same lines is the note in *The Journal of the American Medical Association* on occupational hazards in microbiology.[168]

*Age and Sex Distribution of Patients with Fresh Syphilis.*—Svendsen [169] found that in the cases of early syphilis in the material taken from the monthly list of the Statens Serum Institute, Copenhagen, for 1948 the age of infection was the same as that found by Genner and Lindhardt in 1943 for material from the Department of Dermatology of the Copenhagen City Hospital. He also found a slightly higher average age (rising average age of the population).

*Lesions of the Skull in Secondary Syphilis.*—Utilizing routine roentgenologic examination of the skull in patients with secondary syphilis, Thompson and Preston [170] found an incidence of 8.7% of destructive osteitis of the skull. They point out that occurs more commonly in secondary syphilis than has previously been reported.

*Syphilis of the Breast.*—Anderson [171] notes that chancre of the breast occurs predominantly in women and is a comparatively rare lesion. It occurs mostly from inoculation through kissing by an adult of the opposite sex. The mammary skin is involved in the generalized eruption of secondary syphilis. Diffuse syphilitic mastitis occurs as a very rare manifestation of late secondary syphilis. In neurosyphilis severe recurrent paroxysmal pain in the breast occurs as a rarity.

*Electrocardiographic Changes in Secondary Syphilis.*—Eisenberg and his co-workers [172] performed electrocardiograms on 29 patients with dark-field-positive seropositive secondary syphilis and on 29 normal, nonsyphilitic, persons from the same age and socioeconomic group. Eight of the 29 controls received the same five-day course of penicillin that the syphilitic group received. T wave or S-T segment changes, or both, were found in 7% of the control group and in 38% of the syphilitic group. Of the 11 syphilitic patients with electrocardiographic changes, 9 were improved or normal after penicillin therapy. No electrocardiographic abnormalities were noted due to penicillin alone in the control group.

*Syphilitic Lesions of the Vulva.*—In this general discussion of syphilitic lesions of the vulva, Stevenson [173] discusses their distribution, clinical appearance, inci-

dence, diagnosis, and treatment. Emphasis is placed on careful examination, since genital lesions of syphilis in women are relatively inaccessible and therefore difficult for the patient and the physician to detect.

*Spinal Fluid Examinations Among Patients with Primary or Secondary Syphilis.*—In a most interesting study of spinal fluid examinations in patients with primary or secondary syphilis, carried out before institution of treatment, Bauer, Price, and Cutler [174] found that Group I spinal fluids were observed as frequently in a nonsyphilitic control group as they were in the syphilitic group. This, of course, throws additional doubt on the diagnostic and prognostic import of Group I spinal fluids. Of 12,000 patients, 4.8% had positive spinal fluid tests. The percentage varied by stage, 1.3, 2.9, and 6.1% for seronegative primary, seropositive primary, and secondary syphilis, respectively. Group II or III fluids were observed in 5.4% of the white males, 4% of the Negro males, 2.4% of white females, and 2.8% of Negro females. Of the patients with positive spinal fluids who were subjected to repeat spinal fluid examinations following treatment, results for 86% reversed to negative (93% of Group I fluids; 82% of Group II fluids, and 58% of Group III fluids). The amount of penicillin administered influenced the rate of reversal to negative. In 62% of the patients whose post-treatment spinal fluid was still positive, there was associated infectious or serologic relapse. In only two patients whose spinal fluid remained positive had the blood findings reverted to negative. In patients with initially negative spinal fluid who were subjected to reexamination of the spinal fluid after therapy, 1.2% of the patients with seronegative primary syphilis, 2.8% of the patients with seropositive primary syphilis, and 3.7% of the patients with secondary syphilis developed positive spinal fluids after treatment. With but a single exception all patients with Group II and Group III spinal fluids had associated evidence of reinfection, clinical relapse, serorelapse, or seroresistance. In contrast, 50% of the Group I fluid samples were associated with negative blood tests or a satisfactorily declining titer. This also throws doubt upon the prognostic validity of the Group I spinal fluid.

### RELAPSE AND REINFECTION

Marcussen and Keldbeck [175] noted that 38.8% of patients with gonorrhea had had more than 1 infection; 2.1%, more than 5 infections, and 0.5%, more than 10 infections. The mean interval between two infections varied from 4.7 to 0.7 years, according to the number of infections. Fifty per cent of patients with five gonorrheic infections had had a syphilitic infection; 20% had an early infectious eruption. Two eruptions of primary-secondary syphilis had occurred in 3.9% of patients with early infectious syphilis; most likely, all were reinfections. The mean interval between two syphilitic infections was 11.4 years. Nine-tenths of a per cent (0.9%) of patients had had two syphilitic infections at an interval of less than four years; 0.4%, at an interval of less than three years.

*Second Infection in Treated and Untreated Congenital Syphilis.*—Five cases of reinfection in congenital syphilis are added by Grimble and Hahn [176] to the four previous cases reported by Hahn and Allison. It is of interest that these nine cases, comprising the only indisputable cases of reinfection in congenital syphilis in the literature, were all seen at the Johns Hopkins Hospital. The fact that this hospital serves as a family hospital for many of the residents of Baltimore and, more impor-

tantly, the fact that a unit history system has been vigorously maintained for many years accounts for this unusual circumstance. Three of the five patients had begun treatment within the first year of life, one at age three. These four patients, therefore, presumably cured early in the course of their congenital infection, were susceptible to reinfection many years later. The additional case, however, had never been treated and therefore falls into the very rare of group of superinfection, resulting probably from a first infection with a poorly immunizing strain of treponeme and a second infection with a highly virulent strain.

### LATENT SYPHILIS

As previously stated, there is great need for a definitive study on latent syphilis. None such was presented in the present review period. Barnett,[177] who for many years has been a student of this phase of the disease, points out that the diagnosis of latent syphilis is uncertain because the standard serologic tests are nonspecific and penicillin has not demonstrated its effectiveness in this phase of syphilis. It is necessary, therefore, to continue the public health attack against the symptomatic phases of the disease until diagnostic and therapeutic procedures become more certain.

### LATE SYPHILIS

In this review period only sketchy reports, chiefly of unusual cases of late manifestations of syphilis (other than cardiovascular syphilis, neurosyphilis, and ocular syphilis), have been published.

*Roentgen-Ray Diagnosis of Late Syphilis of the Skin.*—Bonse[178] reports on the soft-roentgen-ray studies in late syphilis of the skin. He feels that the findings are characteristic (vessel changes). Therapeutic effects also show manifest roentgen changes.

*Paroxysmal Cold Hemoglobinuria.*—The history of paroxysmal hemoglobinuria is briefly considered by van Loghem and his colleagues.[179] In 1948, Becker divided paroxysmal cold hemoglobinuria (P. C. H.) into (1) P. C. H. with positive Donath-Landsteiner reaction and positive STS and (2) P. C. H. with negative Donath-Landsteiner reaction and negative STS but marked by a high titer of cold agglutinins. The differential diagnosis is made as follows:

| "Classic" P.C.H. (A) | P.C.H. Caused by Cold Agglutinins (B) |
|---|---|
| 1. No cold agglutinins in high titer | 1. Cold agglutinins in high titer present |
| 2. Donath-Landsteiner reaction positive | 2. Donath-Landsteiner reaction negative or nonspecific |
| 3. Wassermann reaction positive | 3. Wassermann reaction negative or incidentally positive |
| 4. Complement necessary for hemolysis | 4. Complement not necessary for hemolysis |
| 5. Dermolysin present | 5. Dermolysin absent |
| 6. Rashes of cold urticaria frequently observed during attack | 6. No rashes of cold urticaria |
| 7. Vascular disorders absent | 7. Vascular disorders (Raynaud's syndrome) frequently present |
| 8. Antisyphilitic treatment successful | 8. Antisyphilitic and other treatment unsuccessful (in recent publications favorable effect is noticed after combined treatment with vitamin D, estradiol, and thyroid) |

The first group is characterized by a biphasic hemolysin, the second group by the presence of cold agglutinin in very high titer. The authors present three case reports, with extensive serologic studies, one of "classic" P. C. H. and two of P. C. H. caused by cold agglutinins.

The authors stress that

> The hemolysins of Group A, though all of the biphasic type, show many variations as far as concerns thermostability, optimal period of the cold phase and the need of complement for the fixation of the antibody in the cold. In our own case the hemolysin behaved differently from those earlier described in that it reacted only with the patient's cells and not with others. In addition it was found that the hemolysin reacted with P.N.H. [paroxysmal nocturnal hemoglobinuria] cells as a monophasic warm antibody.
>
> Next to the hemolysin an incomplete cold antibody of an unusual type was present in the serum of the patient. It is suggested that this antibody is not identical with the hemolysin and of minor importance for the hemolytic process.
>
> In Group B the cold agglutinins predominated, but apart from these a monophasic warm hemolysin could be demonstrated in the serum of 2 patients.

Complement was found to be reduced or absent in both groups, showing that hemolysins played an active part in red cell destruction, although, of course, cold agglutinins were the most important factor in Group B. Caution was advised in the use of transfusions of fresh whole blood in patients with paroxysmal cold hemoglobinuria and other hemolytic anemias, because the addition of complement might result in the hemolysis of the patient's own red cells as well as those of the donor.

Hall [180] reported a case of paraoxysmal cold hemoglobinuria observed at the Tripler Army Hospital, Honolulu. The patient was a 22-year-old Japanese-Hawaiian, who was seropositive, although he had had 20 injections of an arsenical, 20 injections of bismuth, and 6,000,000 units of penicillin in the preceding five years. The symptoms were produced by the chilling of a Korean winter. Probably the cold-warm hemolysin had long been suppressed because of the mildness of the climate in Hawaii, where the patient had been raised. Hall carefully charted the differences between syphilitic and nonsyphilitic paroxysmal cold hemoglobinuria. That there is a direct etiologic relationship between paroxysmal cold hemoglobinuria of the cold-warm hemolysin type and syphilis is well recognized. The exact role of the syphilitic process, however, is obscure.

*Gumma of Liver Diagnosed by Liver Biopsy.*—Viranuvatti and Kochaseni [181] reported the usefulness of liver biopsy in the diagnosis of gumma of the liver. A 36-year-old Thai woman was admitted to the hospital with a complaint of pain in the right hypochondrium for 15 days. As the result of a positive Kahn test, bismuth salicylate was given intramuscularly. Later penicillin G procaine in oil and beeswax suspension was given. The diagnosis of gumma of the liver was made by liver biopsy. Before the patient was discharged from the hospital, the liver was reduced in size and had become painless.

*Hypopituitarism in Male Subjects Due to Syphilis.*—Oelbaum [182] has described two male patients with Simmond's disease, due in one case to congenital syphilis and in the other to acquired syphilis. It is considered that the lesion affecting the anterior pituitary was fibrotic in nature rather than a gumma (but pathological confirmation is lacking). Treatment with methyl testosterone, 60 mg. daily, was successful in both cases. The literature is reviewed, and the mode of action of the androgen discussed.

*Gastric Syphilis.*—Raffensperger and his colleagues [183] report a patient with gastric syphilis in which an extensive linitis plastica type of lesion was found only 9 to 10 weeks after exposure and 4 weeks after the appearance of the initial genital lesion. Penicillin therapy (6,000,000 units) produced a complete subsidence of subjective complaints and objective findings (gastroscopically) in a period of 10 weeks. Gottlieb and his co-workers [184] also present two cases of gastric syphilis, each with a pyloric lesion. One came to autopsy and was proved pathologically. The other was diagnosed by clinical, roentgen, and laboratory methods, meeting all the recognized and usually accepted criteria for gastric syphilis.

*Late Syphilis of Lung.*—Acquired syphilis of the lung is a rare condition, but the diagnostic criteria are so variable that it is difficult to assess the degree of rarity. It has been stated that the diagnosis cannot be made with assurance during life and is often uncertain at the postmortem examination. The clinical, radiological, and pathological criteria of pulmonary syphilis are discussed in connection with a case of tertiary syphilis of the lung. Morgan and his co-workers [185] conclude that the gumma is the only specific histological criterion of tertiary syphilis of the lung. They say that in a patient with a suggestive clinical picture, positive serological tests, and a sputum persistently negative for tubercle bacilli, if the radiological lesion clears decisively under antisyphilitic treatment, there are reasonable grounds for diagnosing pulmonary syphilis. If as the result of lobectomy or necropsy, typical gummas are demonstrated in the lung, then the diagnosis is virtually certain. As a therapeutic test some investigators have recommended intramuscular injections of bismuth for two or three weeks accompanied by potassium iodide thrice daily and oxophenarsine (Mapharsen) in doses of 0.01 to 0.06 mg. at five-day intervals for 10 to 12 injections. If improvement is satisfactory, treatment should be continued as in other forms of visceral syphilis. In a case recorded in 1947 treatment with penicillin was successful. If the patient fails to respond rapidly, the possibility of neoplasm must be reconsidered, and exploratory thoracotomy or lobectomy may be necessary. If the gummas have permanently damaged the lung, it may be liable to hemorrhage, secondary infection, or bronchiectasis and lobectomy may be advisable. Perdrup [186] likewise has reported a case of presumed bronchial gumma. This was followed up by roentgen ray studies at frequent intervals while it was being treated, first with neoarsphenamine, with inadequate effect, and then with penicillin. The lesion disappeared eight months after the first course of penicillin therapy.

*Infectious Mononucleosis and Syphilis in the Same Person.*—Zarafonetis [187] has encountered an example of the simultaneous occurrence of infectious mononucleosis and syphilis in a 17-year-old girl. Differential diagnosis is sometimes difficult, but serologic follow-up offers a useful approach.

### CARDIOVASCULAR SYPHILIS

*Stethograms in Cardiovascular Syphilis as an Aid for Early Diagnosis.*—In an attempt to diagnose uncomplicated syphilitic aortitis more accurately and earlier, Eisenberg [188] utilized the stethogram (phonocardiogram) in patients with primary and secondary syphilis, in patients with cardiovascular syphilis, and in a normal control group. On the basis of his findings he feels that a systolic aortic murmur and an accentuated second aortic sound are the two important criteria for a diagnosis of uncomplicated syphilitic aortitis. Forty percent of the patients with pri-

mary or secondary syphilis, 62% of the patients with cardiovascular syphilis, and 6% of the normal control group presented one or both of these findings. It is concluded that the stethogram is of help in discovering possible early cardiovascular involvement in the very early stages of syphilitic infection.

*Natural History of Syphilitic Heart Disease.*—Because of the high incidence of syphilis among the Negro population of Charleston, S. C., and its environs, Montgomery and his colleagues [189] have reviewed a large amount of autopsy material and attempted to relate it to the clinical course of the patients before death. The material was drawn from the records of the department of pathology of the Medical College of the State of South Carolina during a 22-year period, from 1928 through 1949. Five hundred fourteen cases were satisfactory for analysis. Auricular fibrillation, bacterial endocarditis, thrombosis and embolism, blood pressure, coronary stenosis, and the course of aortic valve insufficiency are discussed. One of the important aspects of cardiovascular syphilis is the rapid downward course of patients after the onset of aortic valve insufficiency.

*Cardiovascular Syphilis in a General Medical Clinic.*—At the University of California Medical Center, between 1939 and 1951, 354 patients were found by Lucia and his group [190] to have cardiovascular syphilis. Of these, 87.7% were over 40 years of age. Syphilitic aortitis was diagnosed by fluoroscopic evidence of widening of the aorta. Calcification in the wall of the ascending aorta was considered to be oftenest due to syphilis. The syphilitic lesions of the cardiovascular system were classified as simple aortitis, aneurysms, and aortic insufficiency, and the last two combined. Aneurysms were present in 221 (62.4%) of the patients, and in 41 of these the aneurysm was accompanied by aortic insufficiency. On auscultation, aortic insufficiency was revealed in 83 (23.4%) of the patients.

*Syphilitic Heart Disease.*—Pathology, diagnosis, treatment, and course of syphilitic aortitis, uncomplicated aortitis, aortic insufficiency, aneurysm, and stenosis of the coronary artery orifices are discussed by Morgan and Kampmeier.[191] The discovery of penicillin has made the specific treatment of cardiovascular syphilis easy to give and easy to take and has reduced dangerous reactions to a minimum. In spite of the fact that the effectiveness of penicillin therapy of cardiovascular syphilis in persons with latent syphilis has not been conclusively established, the prospects seem bright that the incidence will decrease sharply in the immediate future. Experience thus far does not indicate that penicillin therapy of complications of syphilitic aortitis will be any more successful than was the therapy of the prepenicillin era.

*Syphilitic Aortitis.*—According to Flaum,[192] syphilitic involvement of the aorta begins early in the course of the infection. The aorta is seeded with spirochetes in the primary and secondary stages. At this time, the infection is completely eradicable by adequate antisyphilitic therapy. In untreated syphilis, the aortic infection follows a slow course. Uncomplicated aortitis is the earliest phase of cardiovascular syphilis that may be recognized clinically. Penicillin in oil with 2% aluminum monosterate is used to treat all patients with cardiovascular syphilis.

*Increasing Incidence of Arteriosclerotic Aneurysms.*—A review of the literature and an analysis of the autopsies performed at the Hahnemann Hospital, Philadelphia, are presented by Maniglia and Gregory.[193] Among 6,000 autopsies done from 1906 to 1952, a diagnosis of aortic aneurysm was made in 101 (1.6%).

Since 1931 there has been a steady decrease in the number of syphilitic aneurysms, while the number of arteriosclerotic aneurysms has increased. Evidence is presented which suggests that the reversal in the incidence of the two major causes of aortic aneurysms may be due, at least in part, to a decrease in cardiovascular syphilis and to an increase in the age of the population. Wangensteen and his group [194] presented a case of syphilitic aortic aneurysm with perforation into the gastrointestinal tract, and Levin, Randel, and Ratner [195] report a case, diagnosed during the life of the patient, of gradually developing erosion of a syphilitic aneurysm of the ascending aorta into the right pulmonary artery. Jackson and coworkers,[196] in addition, reported a rare case of superior vena cave syndrome, due to a syphilitic aneurysm with perforation into the superior vena cava. The correct diagnosis was made during the patient's life without the aid of cardiac catheterization or angiocardiography.

## NEUROSYPHILIS

No outstanding study of the clinical manifestations of neurosyphilis has been published in this review period. The data made available, however, are of great interest.

*Syphilis in Mental Deficiency.*—Out of 1,331 mental defectives examined by MacFarlane and Schofield [197] for syphilis, 32 (2.4%) were judged (principally on clinical and serological grounds) to have been infected. The past histories of the patients and their families were also considered. Serological evidence formed the most reliable ground upon which diagnosis could be made. Classical congenital stigmata were present in only 6 patients; altogether, 10 were definitely proved to have the congenital variety of the disease, but in some of the remainder it must be acknowledged that syphilis might have been inherited. There was no reason to suppose that syphilis accounted for mental deficiency to any real extent.

*Tabes Dorsalis in the Native Mohammedan of North Africa.*—Marill, Huguenin, and Khene [198] have detailed their experience with tabes dorsalis in the native Mohammedan of North Africa.

*Electroencephalographic Changes in Neurosyphilis.*—Arentsen and Voldby [199] studied 241 electroencephalograms obtained from 110 patients in the following clinical categories: 35 with dementia paralytica, 24 with taboparesis, 19 with tabes dorsalis, and 32 with other varieties of neurosyphilis. They found a clear difference between the incidence of abnormality in the mainly spinal as compared with the mainly cerebral varieties of the disease. Moderate to severe abnormality occurred in only 9% of the patients with tabes dorsalis, but in 52% of those with dementia paralytica. The incidence of abnormality was found to be much higher among the young than in the old age group, being 81% in those under 40, as compared with 42% in those over 60 years of age. This difference is real and is not a function of duration of the neurosyphilitic symptoms, type of lesion, or type of treatment. The incidence of abnormalities in the EEG is high in the presence of severe mental symptoms.

EEG abnormality is not correlated with abnormal spinal fluid findings, although there is a somewhat higher incidence of EEG abnormality when the spinal fluid and blood serologic tests for syphilis are positive. When the pneumoencephalograms are normal, the incidence of moderate and severe abnormality is 11%, as compared with almost 70% in the presence of ventricular or cortical atrophy.

*The Pupil in Syphilis.*—Jaffe [200] does not believe that syphilis of the brain is a late manifestation of the disease. With regard to the Argyll Robertson pupil, in spite of its outstanding value as a diagnostic sign, little is known of the site of the pathologic disturbance responsible for this phenomenon. Jaffe presents four cases of syphilis with no other evidence of neural involvement than early alterations in the light reflex, demonstrated only by pupilography. Benton [201] points out that in addition to the five criteria for the Argyll Robertson pupil laid down by Douglas Argyll Robertson in 1869 (retina sensitive to light; pupil does not contract on exposure to light, contracts in accommodation, constricts with physostigmine (eserine), but dilates poorly with atropine, and pupil is miotic) three other changes, irregularity of the pupillary outline, loss of the sensory reflex (dilatation of the pupil on pinching the skin of the neck), and atrophic changes of the iris, are found in this condition. Development of the Argyll Robertson pupil progresses through stages that are identical with the seven stages of physiologic fatigue: Diminishing extent of reaction, prolongation of the physiologic latent period between the onset of light stimulation and the beginning of contraction, initial dilatation of small degree preceding contraction, disappearance of the initial dilatation and further prolongation of the latent period, decrease in secondary dilatation following initial contraction, return of initial dilatation followed by no contraction, and complete immobility. Loss of light reflex involves triangular-shaped segments of the iris rather than the entire iris simultaneously. Structural and atrophic changes in the iris include loss of radial folds in the pupillary portion, disappearance of crypts, sector-shaped areas of atrophy, differences in coloration, and irregular pigment deposition over the atrophic segments. The final stage of the Argyll Robertson pupil is complete unresponsiveness of the pupil to light or accommodation-convergence. The site of the lesion causing Argyll Robertson pupil has never been definitely determined. Fanta and Reisner [202] do not believe that the Argyll Robertson syndrome is pathognomonic for neurosyphilis, since they encountered an example of it in a patient with suprasellar tumor. The patient had no evidence of neurosyphilis, and the tumor was diagnosed by surgical intervention.

*Gumma of the Brain.*—Raskin [203] describes in detail a patient with untreated syphilis of long duration, suffering with syphilitic meningoencephalitis and a gumma of the left basal ganglia causing hypothalamic symptoms, hypersomnia, bulemia, polydipsia, polyuria, and obesity.

*Bulbar Palsy Due to Syphilis.*—Cook [204] presents a case of progressive motor nucleus involvement of the lower cranial nerves, with bilateral upper motor neurone signs in arms and legs, due to syphilis. There was considerable improvement during the two years following penicillin therapy. The author points out that all types of nuclear amyotrophy, acute anterior poliomyelitis, amyotrophic lateral sclerosis, progressive muscular atrophy, primary lateral sclerosis, and progressive bulbar palsy may be caused by syphilis. As neurosyphilis is amenable to treatment, all such patients should have blood and spinal fluid examinations before being condemned to a hopeless future.

*Deterioration in Dementia Paralytica.*—Comparative serologic and psychological investigations were made by Kral and Dörken Jr.[205] in 52 institutionalized patients with dementia paralytica, because it is generally accepted that the spinal fluid provides a reliable lead in assessing the effectiveness of the treatment. In

general, it was found that the treated patients with negative spinal fluid reactions showed a more pronounced deficit both of intelligence and of personality resources than those patients still in an active phase of the disease. There was evidence, on the one hand, that part of the impairment of psychological functioning is reversible when the disease process is arrested early in the psychotic stage and, on the other hand, that some of the patients may continue to deteriorate even though treatment has rendered their spinal fluid negative. These results seem to indicate that two pathogenetic factors have to be considered: one probably connected with the inflammatory component and responsible for the acute clinical picture and the pathological changes in the spinal fluid, relatively easily influenced by modern therapeutic methods, and another long-acting, not easily or not at all influenced by therapy, responsible for the slowly progressing deterioration. These are reasons to believe that this second factor is a vascular one, as suggested by Merritt and co-workers.

*Occupational Trophic Ulcer.*—Silver,[206] after an unsuccessful search of the literature for a similar case, reports on a 53-year-old tabetic with an ulcer measuring 10 cm. across, involving the skin and subcutaneous tissues over the greater trochanter. On investigating his history to elucidate the reason for this unusual site for what was apparently a trophic ulcer, it was found that he was a firewood seller and did his rounds with a pony and cart. His usual seat was on the buckboard in front, and he invariably sat on his left buttock and thigh, with his right leg crossed over the left knee. It was thought by Silver that the constant trauma and increased pressure over the greater trochanter, brought about by sitting in this position and constantly mounting and dismounting from the cart, were enough to produce a trophic ulcer. This was particularly likely to occur as he was rather thin and the area involved was anesthetic.

*Masked Abdominal Catastrophe in Tabes Dorsalis.*—Grimble and Csonka § report a case of masked abdominal catastrophe (silent gastric perforation) in tabes dorsalis. They feel that cases of tabes dorsalis with extensive bilateral sensory loss should be investigated with special regard to visceral disease, since the progress of such a condition may be silent.

## OCULAR SYPHILIS

In last year's review we commented on the outstanding contributions dealing with ocular syphilis. The present compilation period contains more of the same, but dealing chiefly with certain specific problems. Again Klauder as well as Oksala have made significant presentations. Cortisone therapy of ocular syphilis has been the subject of a number of contributions.

*Syphilis of the Eye.*—Frequency and importance, clinical manifestations, and treatment of blindness due to syphilis are discussed by Meyer.[209] It is estimated that there are 250,000 industrially blind persons in the United States, of whom 25,000 to 35,000 (10 to 15%) are blind because of syphilis. Case histories of one patient with optic atrophy, one with slowly progressive optic atrophy, and one with preatrophic stage of optic nerve involvement are presented. A study of hundreds of patients at the Wills Hospital, Philadelphia, revealed that optic nerve damage as a result of syphilis was not inevitably followed, sooner or later, by blindness, as was previously assumed.

§ References 207 and 208.

Bagley [210] has analyzed the etiologic factors in a series of 133 cases of optic neuropathies, admitted to the Wilmer Ophthalmological Institute, of Johns Hopkins University and Hospital, between March 1, 1937, and Jan. 1, 1950. Syphilis was considered to be the etiologic factor in 23 patients, of whom 15 showed primary and 6 showed secondary optic atrophy; 1 presented the appearance of a Foster Kennedy syndrome, with primary optic atrophy, and 1 showed unilateral optic neuritis, occurring as a relapse of inadequately treated secondary syphilis.

*Optic Atrophy in Infancy, Childhood, and Adolescence.*—A total of 102 cases of optic atrophy in infancy, childhood, and adolescence were observed by Cordes,[211] at the University of California Hospital, from 1920 to 1950. The etiologic factors in 81 of the patients are discussed. Congenital syphilis was the cause in eight cases of primary optic atrophy and in one case of secondary optic atrophy. The literature on diagnosis, types, and causes of atrophy, including congenital neurosyphilis and syphilis, is reviewed.

*Chorioretinitis of Congenital Syphilis.*—In congenital syphilis the choroid and cornea are most susceptible to syphilitic involvement, its frequency being comparable to that of the osseous system. In this study, 223 patients had interstitial keratitis, while 71 patients with congenital syphilis had not had interstitial keratitis. In the two groups there were 42 patients who had chorioretinitis. Diagnostic features of chorioretinitis are the salt-and-pepper fundus, the peripheral localization of the disease or its predominance in that region, and its association with perivasculitis. Serologic tests for syphilis are not decisive.[212] According to Oksala,[213] the opinion most widely held at present is not that interstitial keratitis and specific chorioretinitis are two distinct conditions. Through a cornea made transparent by means of cortisone, Oksala was able to follow the changes in the fundus of the eye during the active phase of a case of interstitial keratitis associated with congenital syphilis. During treatment the formation of a large patch of chorioretinitis was encountered, thus suggesting a closer relationship than has hitherto been believed to exist between interstitial keratitis and chorioretinitis. Cortisone therapy was of only transient value, since the disease became aggravated fourfold shortly after discontinuance of the cortisone therapy.

*Cortisone Therapy of Ocular Syphilis.*—Ashworth [214] has reviewed the available information on the use of cortisone in the treatment of syphilitic eye disease. He concluded that in cases of ocular inflammation of syphilitic origin the possible benefits of cortisone therapy must be set against the possible effects which systemic cortisone might have on the general syphilis. He stresses the point that cortisone has not cured any condition in which it has been used. It is an adjuvant only to other general and local therapy, which must be actively applied. From the point of view of syphilitic eye disease, this concurrent therapy is possible, since the basic cause of the eye condition is known. Horne [215] points out the possible applications of the hormones in syphilis. The hormones may contribute to the understanding of the disease as well as to its therapy. They have certain usefulness in the various phases of syphilis, especially in ocular syphilis. However, there are definite limitations and potential dangers from their use. Drews and his colleagues [216] used topical cortisone successfully in the management of 18 cases of acute syphilitic interstitial keratitis observed for periods ranging from 2 to 16 months. An occasional severe case may still require artificial fever therapy. At the McPherson Hospital, Durham,

N. C., Chandler, McPherson, and Stocker [217] treated 17 patients with topical cortisone and local atropine for interstitial keratitis. Those who had not received adequate syphilitic therapy were given from 6,000,000 to 8,000,000 units of penicillin. Seven of the patients had recurrences. One patient required six months of treatment before the keratitis could be considered inactive, while in two patients the keratitis was entirely arrested in 10 days. All 17 patients were considered improved. Likewise, Steffensen [218] believes that syphilitic interstitial keratitis responds favorably to topical cortisone.

*New Treatment for Calcific Corneal Opacities.*—A method for dissolving calcific corneal opacities by the use of a solution of the neutral sodium salt of ethylenediamine tetraacetic acid is reported.[219] Treatment with this agent is of value for corneal opacities consisting of calcific deposits in the corneal epithelium or in the anterior layers of the stroma. Opacities in this region may be exogenous, such as those caused by lime burns, or endogenous, as in band keratopathies associated with long-standing uveitis, phthisis bulbi, or hypercalcemia. No effect is to be expected from treatment of noncalcific opacities caused by scarring, edema, vascularization, or infiltration with inflammatory cells. The treatment may have for its purpose the removal of opacities situated in the visual axis or the relief of discomfort during spontaneous extrusion of these calcified particles. A soluble compound of calcium is formed by the action of the substance (EDTA) on the calcific deposits. Since the agent does not penetrate the corneal epithelium, it is necessary to remove such epithelium, unless the calcification extends directly to the surface. Although a number of other agents were found to be effective as regards calcium solubility, EDTA was the least toxic. The area to be treated is irrigated for 15 minutes with a sterile 0.01 molar solution of the drug. Topical anesthesia is used. Six case reports are presented (in treatment of which patients the foregoing procedure was used): two of the lye burns (one of only 20 hours' duration), one of uveitis, one of phthisis bulbi, one of sympathetic ophthalmia, and one of band keratitis in a patient with Hodgkin's disease. There seemed to be no tendency for the deposits to recur in the course of follow-up observations.

## CONGENITAL SYPHILIS

Much material in the section on ocular syphilis deals with congenital syphilitic ocular disease. This section covers a variety of clinical aspects of congenital syphilis.

Gumpesberger [220] uses the term syphilis acquired in infancy for all forms of infantile syphilis not definitely classifiable as congenital syphilis, in which infection takes place during intrauterine life or at birth. Differential diagnosis of acquired syphilis, which offers great difficulties, especially in infancy, is discussed. Careful investigation into the milieu, especially examination of the mother, is considered to be of great importance. Differentiation on the basis of cutaneous and mucosal changes alone is often hardly possible. Radiological skeletal changes are of importance in differential diagnosis only in late childhood, inasmuch as they are not found in older children with acquired syphilis. Prompt reactions to specific treatment are suggestive of acquired syphilis. The author reports on personal observations, made since 1945, on 37 cases (only one nursling): 5 children showed Stage I seropositive syphilis; 28, Stage II, and 3 latent syphilis; one school girl had cranial gumma. In Stage II syphilis, cutaneous and mucosal changes are about

equally frequent. Acquired syphilis was diagnosed with certainty in only 16 children. In the remaining 21, the diagnosis was only tentative. In 29 cases, infection originated from near relatives, predominantly by the extragenital route. Various therapeutic measures to be used in acquired syphilis are discussed. Although the dictum that no syphilitic child may be born without a syphilitic mother is generally accepted, Gaase [221] reports two cases which seem to be contrary to this concept. Oehme [222] points out the changes which have occurred in the diagnosis of congenital syphilis occasioned by the diminution of signs due to therapy (preventive) and the occurrence of diseases (histoplasmosis, etc.) which must be differentiated from syphilis. Cernea [223] has presented a short summary of the diagnosis, differential diagnosis, and clinical manifestations of congenital syphilis of the ear.

*Cogan's Syndrome.*—Oliner and his co-workers,[224] who presented a case of nonsyphilitic interstitial keratitis with deafness (Cogan's syndrome) associated with periarteritis nodosa, suggested that the syndrome is only a localized manifestation of essential polyangitis.

Of 59 instances of congenital syphilis, examined roentgenologically by Engeset and co-workers,[225] at the University Hospital, in Oslo, 31 presented pathologic skeletal changes, while 18 were normal. The authors concluded that the skeletal changes are best explained as disturbances in bone growth of quantitative and qualitative nature and not as destructive and specific changes. As a rule, changes in early congenital syphilis heal without leaving scar or deformity.

*Congenital Syphilis and Scurvy as Causes of Painful Joints in Childhood.*—Mukherjee [226] found one case among four of painful joints in infancy due to syphilis; the other three were caused by scurvy. These lesions are presumed to be more common than is usually supposed.

*Dental Stigmata of Prenatal Syphilis.*—Bradlaw [227] found the usual explanations for the dental stigmata of prenatal syphilis to be inadequate. Theoretical considerations support the hypothesis that the tooth germs are affected before calcification begins. Those of the affected teeth develop approximately between the fourth and sixth months in utero, which is exactly the time when placental changes permit fetal infection to take place. T. pallidum has not been recorded in the fetus of less than 16 to 18 weeks. If the cause of the dental stigmata is a disturbance of the dental formation cells before calcification takes place, it would at once explain why the deciduous teeth are unaffected, for their tooth gums are fully differentiated by the 10th week of uterine life, and why many who have had early florid manifestations of prenatal syphilis have no dental abnormalities. Histologic studies show that this theory is correct. T. pallidum may be found throughout the developing tooth germ in prenatal syphilis. It may be seen in and around the follicular blood vessels and in their walls in the dentine papillae and in the dentine. Progressive pathologic changes have to be characteristic dental deformities.

*Causes of Fetal and Neonatal Death with Special Reference to Pulmonary and Inflammatory Lesions.*—A detailed report is presented by Arey and Dent,[228] based on the consecutive autopsy records of 35 nonmacerated fetuses and 102 liveborn infants dying in the neonatal period on the Tulane Service of the Charity Hospital of Louisiana, New Orleans, between September, 1945, and October, 1947. An adequate anatomic cause of death was demonstrated in 107 infants and fetuses, i. e., in 87 of the liveborn infants and in 20 of the stillborn fetuses. Anatomic causes of

death are listed in a table, and material on deaths in each group discussed separately. Congenital syphilis was responsible for nine fetal and neonatal deaths. Five additional infants had gross and/or microscopic findings which were probably the result of congenital syphilis, but in these a positive diagnosis could not be established. Among the nine fetuses and infants dying as a result of congenital syphilis, there were eight liveborn premature infants and one stillborn full-term fetus. All the members of this group were Negro. Histopathologic findings are described. An extensive review of the literature is given, and a bibliography of 129 references is appended.

*Third-Generation Syphilis.*—Wright and Inoue [229] have presented another case of probable third-generation syphilis, uncovered in a family study tracing a syphilitic infection from grandparents to mother to infant. They believe that the data presented fulfill the rigid criteria necessary for a diagnosis of a case of third-generation syphilis.

*(To be concluded)*

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# Case Reports

## MENINGITIS TREATED WITH DIETHYLAMINOETHYL ESTER HYDRIODIDE OF PENICILLIN G (NEO-PENIL)

### Report of Two Cases

CRAIG N. SMITH, M.D.
AND
JOHN STAIGE DAVIS Jr., M.D.
NEW YORK

IN AN ATTEMPT to develop a long-acting repository form of pencillin various modifications of ordinary benzyl penicillin have been prepared in an effort to maintain suitable therapeutic concentrations in the body. Jensen and his co-workers * in 1948 successfully developed a diethylaminoethyl ester hydriodide of penicillin G which, although it was found in low cencentrations in the plasma after intramuscular injection, did appear in high concentrations in sputum and lung tissue. This was ascribed to a specific organ affinity of the unhydrolyzed ester, which on hydrolysis in lung tissue liberated free penicillin and diethylaminoethyl alcohol. Comparison studies † in patients with equal amounts of penicillin procaine, penicillin sodium, and the diethylaminoethyl ester hydriodide of penicillin G revealed a five to eight times greater sputum concentration with the latter drug.

Animal studies have shown [6] unusually high penicillin concentrations in the brain tissue of those treated with this ester. More important, Wellman and co-workers [7] in a comparison study in humans of Neo-Penil,‡ penicillin G procaine, chlortetracycline (Aureomycin), oxytetracycline (Terramycin), dihydrostreptomycin, and erythromycin found that of all these "only Neo-Penil and aureomycin can be detected consistently in significant amounts in the brain tissue."

Schimmel and his co-workers [8] reported that one-hour spinal fluid levels determined for 28 patients treated for neurosyphilis revealed that Neo-Penil achieved spinal fluid concentrations approximately 10 times higher than those achieved by equal doses (given to the same patients) of penicillin G procaine, penicillin G potassium, or dibenzyl penicillin G. They were not able to state definitely that Neo-Penil had hydrolyzed to free penicillin in the spinal fluid, but they assumed that hydrolysis had occurred, as it does in lung tissue.

The implications of this, however, have created a great deal of interest, as it is now well known that penicillin administered parenterally does not readily diffuse across the thecal barrier. Because of this, penicillin has been administered intrathecally, to the great discomfort of the patient, and adverse complications have resulted from this method. But if a penicillin ester, such as Neo-Penil, may be

From the Department of Medicine, St. Luke's Hospital.

* References 1 and 2.

† References 3-5.

‡ Neo-Penil is the trademark of Smith, Kline & French Laboratories, Philadelphia, for the diethylaminoethyl ester hydriodide of penicillin G.

administered intramuscularly and produce sufficiently high concentrations in the spinal fluid, then such an antibiotic might prove a useful adjunct to the treatment of bacterial meningitis.

We are presenting here two cases of bacterial meningitis treated with combined therapy in which unusually high spinal fluid levels of Neo-Penil were obtained.

CASE 1.—A 65-year-old white spinster was admitted to St. Luke's Hospital on Jan. 8, 1953, after having been in a febrile comatose state for two days. The patient had lived alone in a downtown hotel room and had been in good health save for a five-year history of elevated blood pressure and dizziness. Approximately three weeks prior to admission she was seen by a physician because of right-sided earache, deafness, and fullness in her head. She was examined, was given three injections of penicillin procaine over a six-day period, and presumably did well. Two days prior to admission she was found by the hotel chambermaid to be lethargic and acutely ill. The hotel nurse was called and found the patient to have a temperature of 104 F. She referred the patient to her private physician. The patient was seen by him that evening in a confused febrile state and complaining of low-back pain. Because she was a Christian Scientist, she refused to be admitted to the hospital. She was given 400,000 units of penicillin procaine and on the following day was found to be markedly dehydrated, disorientated, and incontinent of urine. When physical examination revealed crepitant rales in the base of the right lung posteriorly, immediate admission was advised.

On admission the patient was noted to be an elderly moderately dyspneic white woman in a semistuporous state, responding only to painful stimuli. Her temperature was 104.2 F., pulse rate 120, and blood pressure 190/80. Her respirations were rapid and shallow, and her skin was hot and moist. Her pupils were round, regular, and equal and reacted to light and in accommodation. There was a Grade II retinopathy bilaterally. Her right ear drum was swollen, tense, and injected, with obliteration of the landmarks. The left drum revealed an area of injection over Shrapnell's membrane. The tongue was dry, cracked, and coated; the mucous membranes were dry. The lungs revealed an area of moist inspiratory crepitant rales in the right base posteriorly below the level of T-5. The left lung was clear to percussion and auscultation. The heart was enlarged to the left. The sounds were of good quality with normal sinus rhythm. There was a Grade II blowing systolic murmur heard over the entire precordium, but it was loudest over the second left interspace. The abdomen was soft and pliable, with no palpable masses. The liver, spleen, and kidneys were nonpalpable, and normal bowel sounds were heard throughout. There was no edema of the extremities, and the dorsalis pedis pulsations were palpable bilaterally. The results of vaginal and rectal examinations were within normal limits. Neurological examination revealed a moderate amount of nuchal rigidity with positive Brudzinski and Kernig signs bilaterally. There were bilateral hypoactive reflexes of the lower extremities, more marked on the right. Laboratory tests revealed the following: urinalysis, normal; RBC, 4,530,000; hemoglobin, 13.1 gm.; WBC, 14,700 (87% polymorphonuclear cells, 5% band cells, 6% lymphocytes, and 7% monocytes); $CO_2$-combining power, 46 vol. %; BUN and blood sugar, normal. Initial lumbar puncture revealed turbid pinkish spinal fluid; the initial pressure was 150 mm.; cells were 2,400, of which 1,650 were polymorphonuclear leucocytes. Protein was 425 mg., sugar 56 mg., and chlorides 700 mg. per 100 cc. Three spinal fluid and four blood cultures were sterile. Nose and throat cultures revealed only normal flora. A chest film taken one week after admission revealed only a moderately enlarged heart and a calcified aorta. An electrocardiogram revealed a sinus tachycardia, rate 105, and an intermediate electrical axis.

On admission the patient was given Neo-Penil, 1,000,000 units twice a day intramuscularly and sulfisoxazole (Gantrisin), 8 gm., in molar lactate solution intravenously each day. Her temperature (which had been 104.2 F.) fell to normal by the fifth hospital day, when the patient began taking fluids by mouth. A repeat lumbar puncture done on the sixth hospital day revealed a Neo-Penil level of 0.96 units per cubic centimeter, with clear fluid and normal protein and glucose values. On the seventh hospital day, however, the patient's temperature rose to 102 F. and continued to remain elevated, although adequate serum and spinal fluid levels of sulfisoxazole and Neo-Penil were being obtained. A third lumbar puncture, done on the 14th hospital day, revealed a Neo-Penil level of 0.12 units per cubic centimeter. The blood

Neo-Penil level at this time was 0.96 units per cubic centimeter. The patient was continued on parenteral fluids, and her serum electrolytes were rectified on several occasions by means of potassium and saline supplements. On the 14th hospital day the patient became very dyspneic and rales developed in her lung bases; she was digitalized and improved. Her fever, however, persisted until the 16th hospital day, when sulfisoxazole was stopped. It was presumed to be a drug fever, since after sulfisoxazole administration was stopped her temperature fell to within normal limits. She was able to sit up in a chair and improved steadily. X-rays of her mastoid bones revealed an over-all density of the right mastoid process, with thickening of the mucous membranes, and it was thought that this probably provided the focus of infection. She was continued on Neo-Penil and was transferred to the ear, nose, and throat service, where a right mastoidectomy was done on the 48th hospital day. The patient was discharged on the 10th postoperative day.

CASE 2.—A 60-year-old white broker was admitted to St. Luke's Hospital on Jan. 7, 1953, after having had Jacksonian convulsions for three hours prior to admission. The patient had been admitted to St. Luke's twice previously; the first admission was in April, 1950, when he was found to have a right lower lobe pneumonia and a purulent meningitis of undetermined origin. His second admission was in March, 1952, when he was found to have a Pneumococcus meningitis Type III and left acute catarrhal otitis media. His history revealed that in 1946 he had been operated on at another hospital for a left parasagittal meningioma. Thereafter he had had occasional episodes of Jacksonian epilepsy, which were well controlled with diphenylhydantoin (Dilantin) and phenobarbital save for the two episodes of recurrent meningitis treated in this hospital. Since the patient's last admission, in March, 1952, he had had no difficulties until the day of admission, when he noted the onset of a blowing sensation in his left ear and a feverish feeling. He was seen in the emergency room of St. Luke's Hospital, where he was found to have a temperature of 98.6 F. and an acutely inflamed left eardrum. He was given 300,000 units of penicillin procaine and returned home. That afternoon, however, he developed a series of Jacksonian seizures, became unresponsive, and lapsed into coma.

On admission he was acutely ill and was actively convulsing, with focal seizures of the right arm and leg. His temperature was 100.4 F., pulse rate 100, respirations 24, and blood pressure 154/80. There was a left-sided bony defect of the parietal area and an opacity of the left lens. The pupils were round, regular, and equal, but they reacted sluggishly to light. The right retina was visualized and appeared normal. The left eardrum was inflamed, tense, and bulging, with obliteration of the landmarks. The pharynx was injected; there were some enlargement and hyperemia of the left tonsil. The lungs were clear to auscultation and percussion. The heart was not enlarged to percussion; the sounds were of good quality, with normal sinus rhythm. There were no shocks, murmurs, or thrills. The abdomen was soft and pliable. There were no palpable masses; the liver, spleen, and kidneys were nonpalpable. Rectal examination and examination of the genitalia revealed nothing. Neurological examination revealed bilateral hyperactive reflexes after convulsions; there was no nuchal rigidity. Brudzinski and Kernig signs were not elicited.

Laboratory tests revealed the following: urinalysis, albumin 3+; RBC, 6,090,000; hemoglobin, 17.9 gm.; WBC, 25,000 (92% polymorphonuclear cells, 10% band cells, 6% lymphocytes, and 2% monocytes); blood sugar and blood urea nitrogen, normal. A lumbar puncture done on admission revealed cloudy spinal fluid. The initial pressure was 260 mm. $H_2O$. There were 7,500 cells per cubic millimeter, with 1,450 red blood cells and 6,050 white blood cells, 100% of which were polymorphonuclear leucocytes. Smear and culture of this material revealed Pneumococcus Type XII. Sensitivity tests of this isolated organism revealed it to be susceptible to penicillin, sulfisoxazole, chlortetracycline, chloramphenicol, bacitracin, and oxytetracycline and resistant to sulfadiazine. Throat culture revealed Neisseria catarrhalis, Micrococcus tetragenes, and Bacillus proteus vulgaris.

Chest x-ray revealed the heart and aorta to be within normal limits, with no evidence of parenchymal infiltration. The electrocardiogram showed only a sinus tachycardia, rate 120, and left axis deviation. X-ray of the mastoid areas revealing considerable haziness of the air cells of the left mastoid was suggestive of an acute process. Skull x-rays showed that a portion of the bony tables in the posterior frontal and anterior parietal region of the left side had been surgically removed.

On admission, the patient's seizures were controlled by phenobarbital sodium and intravenous amobarbital sodium (sodium amytal) and he appeared to be doing well. On the second hospital day, however, his temperature rose to 103.8 F. He was placed on Neo-Penil, 500,000 units every six hours intramuscularly; sulfisoxazole, 4 gm. by mouth, and sulfadiazine, 5 gm. intravenously. At this time he had developed clinical signs of meningitis as manifested by a stiff neck and positive Kernig and Brudzinski signs. A myringotomy was done on the left drum, but cultures of this fluid proved negative. Because of the resistance of the organism to sulfadiazine, the patient was continued only on Neo-Penil, 500,000 units every six hours intramuscularly, and sulfisoxazole, 8 gm. (2 gm. every six hours by mouth). On the fourth hospital day, in spite on an elevated temperature, ranging between 102 and 103 F., the patient had no clinical evidence of meningitis and his sensorium was clear. On his seventh hospital day a repeat lumbar puncture was performed. The initial pressure was 260 mm. of water; the fluid was clear and colorless. There were 29 cells, 15 of which were white blood cells (85% polymorphonuclear cells). Protein was 77 mg., and sugar, 59 mg. per 100 lb. The spinal fluid Neo-Penil level was 0.48 units per cubic centimeter. The patient continued to do well; his temperature fell to normal by the eighth hospital day, when sulfisoxazole was stopped. He was continued on Neo-Penil, however, until the 18th hospital day, when he was transferred to the ear, nose, and throat service for a possible mastoidectomy. Surgery, however, appeared unnecessary, and he was discharged on his 38th hospital day, improved.

SUMMARY

Two cases of bacterial meningitis successfully treated with sulfisoxazole (Gantrisin) and the diethylaminoethyl ester hydriodide of penicillin G (Neo-Penil) are presented. In both these cases exceptionally high spinal fluid levels of Neo-Penil were obtained. It is suggested that Neo-Penil may prove to be a useful therapeutic adjunct in the treatment of bacterial meningitis.

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# Case Reports

## RUPTURE OF SPLEEN IN SUBACUTE BACTERIAL ENDOCARDITIS

### Mycotic Aneurysm of Splenic Artery and Spontaneous Rupture of Spleen in Subacute Bacterial Endocarditis

WALTER S. WOOD, M.D.
AND
BUFORD HALL, M.D.
CHICAGO

THE ASSOCIATION of bacterial endocarditis and mycotic aneurysm has been recognized for over a century. In 1851, Koch [1] described a patient with endocarditis who died suddenly after rupture of a superior mesenteric artery aneurysm. Tufnell [2] recognized the influence of emboli from valvular vegetations in the development of arterial aneurysms. Osler [3] termed these emboli "mycotic" and postulated the significant role of micro-organisms in the production of such aneurysms. In his Gulstonian Lecture on Malignant Endocarditis,[4] Osler described a case of "ulcerative endocarditis," with multiple small aneurysms involving the aortic arch. In 1887, Eppinger [5] demonstrated the actual infectious nature of the emboli, applying careful bacteriologic techniques.

We are reporting a patient who recovered from subacute bacterial endocarditis complicated by a ruptured aneurysm of the splenic artery and rupture of the spleen.

#### REPORT OF A CASE

V. C., 401163, a 30-year-old white housewife, was admitted to the Research and Educational Hospital on March 31, 1953, and was discharged on June 25, 1953. She gave a history of some aching in the legs between the ages of 8 and 10 years and had had a known cardiac murmur for three years. She had been generally well, however, until about nine months prior to admission (June, 1952), when she noted undue fatigue, mild exertional dyspnea, and slight ankle edema. Treatment consisted of vitamins and thyroid extract without notable improvement. In September, 1952, hemorrhoidectomy was performed at the Decatur County Hospital. After her discharge from the hospital, a persistent cough developed, which was accompanied by several episodes of streaky hemoptysis, drenching night sweats, daily fever, and weight loss. The fatigue, dyspnea, and ankle edema became severer. The patient returned to the hospital in November, and examination revealed an oral temperature of 101 F., pulse rate of 128, blood pressure of 104/65, pallor, and pitting edema. The spleen was palpable, and a tender liver edge was felt on full inspiration. A loud mitral systolic murmur was present. Laboratory examinations revealed a hemoglobin of 10 gm. per 100 cc., a red blood cell count of 3,400,000 per cubic millimeter, a sedimentation rate of 55 mm. in one hour by the Westergren method, and two to three erythrocytes per high-power field in the urinary sediment. A Gram-positive organism with the cultural characteristic of a Staphylococcus was grown from the blood. Sensitivity studies by the disc method showed an 8 mm. zone of inhibition with chloramphenicol, 1 mm. with chlortetracycline (Aureomycin), and 2 mm. with oxytetracycline (Terramycin). No inhibition occurred with penicillin or streptomycin. Treatment included 1,000 cc. of whole blood and 2,000,000 units of penicillin intramuscularly with 2 gm. of chloramphenicol by mouth daily for 24 days in the

From the Research and Educational Hospitals and the Department of Medicine, University of Illinois College of Medicine.

hospital and 1 gm. of chloramphenicol daily for an additional 10 days following discharge. The temperature remained below 99 F. during the last two weeks of hospitalization, and a blood culture was sterile.

The patient felt generally improved after discharge, although she still complained of weight loss, fatigue, and weakness. After an upper respiratory infection in December, she was hospitalized a third time, because of persistent low-grade fever. A "mildly hemolyzing Staphylococcus" was again obtained on blood culture, which now was sensitive only to erythromycin (disc method). Clubbing of the fingers was noted at this time. The patient was treated with 750 mg. of erythromycin orally and 1 gm. of chloramphenicol orally daily for 18 days in the hospital, and erythromycin was continued on an outpatient basis for three additional weeks. While hospitalized, she received the fifth blood transfusion since the onset of her illness. However, she continued to feel unwell and had occasional elevations of temperature to 100 F. during the three months before admission to Research and Educational Hospital. For several days before entering she complained of severe, constant left upper quadrant pain which radiated to the shoulder.

Physical examination at the time of admission revealed a pale, thin, chronically ill woman complaining bitterly of abdominal pain. The rectal temperature was 99 F., the blood pressure 108/58, pulse rate 86, and respirations 24 per minute. Scattered petechiae, moderate clubbing of the fingers, and subungual splinter hemorrhages were present. The heart was slightly enlarged, with a Grade 3 systolic and a faint rumbling diastolic murmur at the apex. The spleen was moderately enlarged to palpation and quite tender.

On admission, results of urinalysis were normal except for rare erythrocytes in the sediment. The hemoglobin was 12.5 gm. per 100 cc.; the hematocrit level, 36%, and the leucocytes 7,160 per cubic millimeter. The sedimentation rate was 44 mm. in one hour by the Wintrobe method. The blood nonprotein nitrogen was 25 mg. per 100 cc. The serum electrolytes were normal. An electrocardiogram was within normal limits. A roentgenogram and fluoroscopy of the chest disclosed left ventricular and left atrial enlargement. Five successive blood cultures revealed growth of an Enterococcus. Determinations by the serial two-fold tube-dilution method revealed the organism to be sensitive to 15.6 $\gamma$ per cubic centimeter of chlortetracycline, less than 0.12 $\gamma$ per cubic centimeter of erythromycin, 31.3 $\gamma$ per cubic centimeter of streptomycin, and 3.9 $\gamma$ per cubic centimeter of penicillin. Diagnoses of rheumatic heart disease with mitral regurgitation and stenosis, bacterial endocarditis due to an Enterococcus, and probable splenic infarcts were made. The patient was given 6,000,000 units of an aqueous solution of penicillin G potassium intravenously in each 24-hour period with 2 gm. of probenecid (Benemid) orally and 1 gm. of streptomycin intramuscularly daily. This therapy was continued for a period of nine and one-half weeks. From April 8 to 13, while the patient was recovering from splenectomy, the penicillin dosage was increased to 12,000,000 units in each 24 hours.

One week after admission the patient complained of a sudden marked increase in the severity of her left upper quadrant pain. Within 30 minutes she became increasingly pale, dyspneic, and anxious and complained of thirst and tenesmus. Examination disclosed an irregular, weak pulse of 40 per minute and a blood pressure of 60/0. The abdomen was extremely tender in the left upper quadrant, and percussion suggested fluid in the left flank. The hematocrit level had fallen to 17% and the hemoglobin to 5.5 gm. per 100 cc. A diagnosis of splenic rupture was made. As preparation for surgery, phenylephrine hydrochloride (Neo-Synephrine) and arterenol (Nor-epinephrine; Levophed) were administered, together with 3,000 cc. of whole blood intravenously under pressure. At the start of the operation, the blood pressure was 110/50 and the hematocrit reading was 42%. The peritoneal cavity was cleared of fresh partially clotted blood, revealing an enlarged, soft, lacerated spleen, which was resected without difficulty.

The pathology report was as follows*: The spleen weighed 500 gm. and measured 14 by 9 by 6 cm. In the midportion, opposite the hilar area, there was a 4 cm. long deep irregular laceration, which was seen to extend into an infarcted area. In the deeper portion of the infarcted area in which the laceration occurred there was a soft hemorrhagic area, which appeared to be of recent origin. In one of the branches of the splenic artery in the hilar region an aneurysmal dilatation occurred, which measured 2.5 cm. in diameter. The aneurysm extended into the parenchyma. The wall was irregular and thin, and the cavity was filled with clotted blood. In the superior portion of the aneurysm was a small fold, leading to a smaller, secondary aneurysmal

* Dr. Cecil Krakower, Department of Pathology, assisted in the pathology examination.

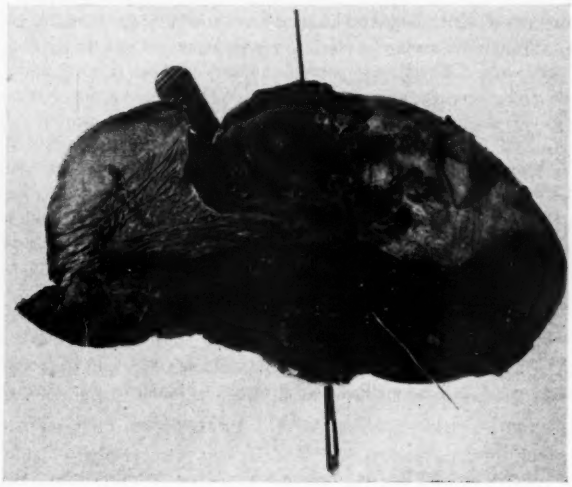

Fig. 1.—Gastric surface of the spleen, formalin-fixed. The probes cross in the bed of the aneurysm, situated in the region of the splenic hilum. The vertical probe passes through a slit-like laceration in the superior portion of the aneurysm and passes through the area of rupture, as seen in Figure 2. The horizontal probe enters a smaller secondary aneurysmal dilatation.

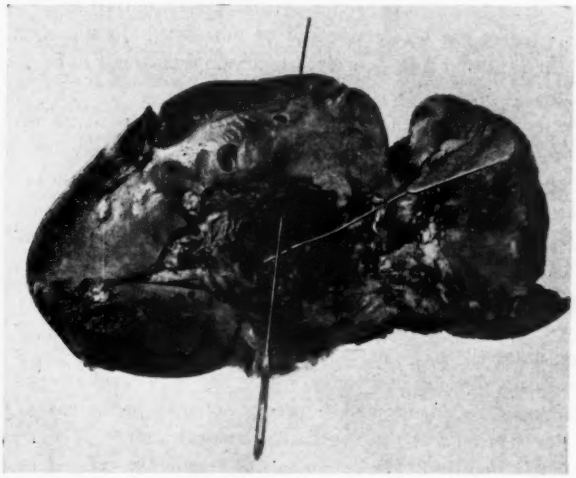

Fig. 2.—Diaphragmatic surface. For the purpose of visualization, the lower third of the splenic parenchyma has been resected. The vertical probe emerges through the deep irregular laceration, which is located within an area of infarction. Directly beneath the rupture, the second probe emerges from the secondary aneurysm.

dilatation. At one point in the primary aneurysmal sac there was a small slit, 2 to 3 mm. in length, which communicated with the lacerated splenic parenchyma and appeared to be the site of rupture of the vessel wall. The two aneurysms were immediately adjacent to one of the infarcts. Section through the aneurysm showed a wall composed of cellular fibrous tissue overlaid by recent blood clots. The adjacent parenchyma was fibrosed (Figs. 1 and 2).

Convalescence from surgery was proceeding uneventfully until one week postoperatively, when alternating diarrhea and constipation appeared, associated with painful defecation. Rectal examination revealed a second degree prolapse with rectal fissure and constriction. Because of continued severe rectal pain, hemorrhoidectomy, with repair of the rectal prolapse, was performed on May 29.

All blood cultures were negative after the onset of treatment. However, culture of the splenic tissue removed at operation revealed growth of an Enterococcus with sensitivities similar to those obtained on the organism recovered in the blood stream. All antibiotic therapy was discontinued on June 11, and the patient was discharged on June 25 without complaints. As of Oct. 12, 1953, there was still no clinical evidence of relapse. Her weight had increased to 118 lb. (53.1 kg.), representing a gain of 28 lb. (12.6 kg.) since admission to the hospital. The hemoglobin was 12 gm. per 100 cc., the hematocrit reading 39%, and the sedimentation rate 2 mm. in an hour by the Wintrobe method. No growth of organisms was obtained with repeated blood cultures.

## COMMENT

Sherlock [6] noted a 0.039% incidence of splenic artery aneurysm of combined etiology, in 8,400 autopsies. Garland [7] found three cases in 4,100 autopsies at the Massachusetts General Hospital. As of 1947, there were 144 cases of ruptured splenic artery aneurysms reported, and of these Cosgrove [8] analyzed 107. Of 98 patients whose sex was reported, 60 were female, and 15 of these were pregnant. The relatively high incidence among pregnant females has been frequently noted.† The cause was determined to be bacterial endocarditis in one of the 15 patients. In the remainder, the origin was congenital or not stated. In the combined series of 107 patients, the ruptured splenic artery aneurysm was found to be of mycotic origin in 19% of cases.

In a collected series of 150 autopsies performed on patients who died of subacute bacterial endocarditis, Blumer [14] found an incidence of mycotic aneurysm in 6%. In the review by Stengel and Wolferth [15] of 217 cases of mycotic aneurysms, bacterial endocarditis was present in 187. The aneurysms were multiple in 23%. Vessels throughout the entire arterial system may be involved, from the aorta [16] to the smallest arterioles. In the above 217 cases, the aorta was involved in 64 and the main intra-abdominal branches were next in frequency. There were 15 collected cases involving the splenic artery or its main branches. The intracranial arteries were involved in 34 cases, the most frequent being the middle cerebral. Mycotic aneurysms develop less commonly in the peripheral arteries.‡ The heart is frequently damaged by aneurysms, occurring not only in the valves but also in the interventricular septum and the ventricular myocardium.[19] The sinus of Valsalva is also frequently involved.[2] In reviewing 442 penicillin-treated cases of subacute bacterial endocarditis, Cates and Christie [21] found hemorrhage from the rupture of a mycotic aneurysm to be the chief cause of death in 17 and a contributory cause in 3 additional cases. Of these 20 cases, the cerebral artery was affected in 16, the mesenteric artery in 2, the femoral artery in 1, and a vessel of the pericardium in 1.

† References 9-13.

‡ References 16-18.

Compared with aneurysms of other etiology, those of mycotic origin tend to be small and multiple. Development is relatively rapider. Both the acute ulcerative and the chronic, or healing, stages may be demonstrated in the same patient. Mycotic aneurysms form at the site where emboli have a tendency to lodge, such as at bifurcations, sharp angulations, sclerotic plaques, and points where the caliber of an artery suddenly narrows. The formation of an aneurysm is esentially dependent upon the destruction of the internal elastic membrane, although the media and adventitia may also be injured. Direct intimal implantation of emboli is the more important, but the infected emboli can be seeded within the arterial wall by way of the vasa vasorum.[22] Bacterial invasion may also occur by direct contiguity of the vessel with an extrinsic inflammatory area such as a pyogenic abscess or cavity. The progressive dilatation of an aneurysm depends not only upon the intrinsic inflammatory process but also upon the resisting strength of the supporting structure.

The signs and symptoms associated with a mycotic aneurysm depend essentially upon the vessel involved and the structures secondarily affected. Because of their small size they frequently remain silent; however, if of sufficient size, a pulsating mass with a systolic bruit may be found. When an extremity is involved by the seating of an embolus, pain, swelling, and redness may be present, simulating phlebitis. If thrombus or rupture occurs in the involved arterial segment, the pulse may be weakened or absent. Involvement of the cerebral arteries can simulate a cerebral vascular accident.[23] Mycotic aneurysms of the intra-abdominal arteries are likely to be silent. In Sherlock's series of splenic artery aneurysms of combined etiology,[6] 34% of the patients had abdominal pain, usually confined to the left upper quadrant and paroxysmal in character. The spleen was palpable in 18% of the total group. It is not unusual for a patient to develop shock from rupture of a splenic artery aneurysm without premonitory symptoms. Rupture may occur in two stages: first, a slow leakage into a limiting surrounding of adhesions or into the lesser peritoneal sac, later followed by a massive rupture, with sudden vascular collapse.[24]

We have been unable to find any previously reported cases of ruptured mycotic aneurysm of the splenic artery associated with rupture of the spleen. It is surprising that splenic rupture does not occur more frequently in bacterial endocarditis, for splenomegaly is present in 60% and splenic infarcts in 40 to 60%.[25] Of the 11 previously reported cases § the rupture resulted in death in all but 1 case. In the single exception [26] the patient died subsequent to other complications nearly a year after successful splenectomy. The specific diagnosis of splenic rupture as due to bacterial endocarditis was made during life in only one case. In all cases, shock immediately followed rupture. It was associated with massive intraperitoneal hemorrhage in eight cases and with the combination of acute suppurative peritonitis as well as hemorrhage in three. Rupture occurred in an infected infarct or frank abscess in six of the 11 cases.

The clinical picture created by rupture of the spleen is usually one of sudden massive intraperitoneal bleeding producing signs of progressive peritoneal irritation and shock. As in splenic infarction, pain is severe and abrupt, often referred to the clavicles or left shoulder. An early sign of diagnostic aid is the increased size of percussible splenic dullness. A plain film of the abdomen may show increased

§ References 26-36.

opacity in the left upper quadrant accompanied by an indistinct splenic shadow. As in rupture of a splenic artery aneurysm, splenic rupture may occur in two stages.[37] At first, the pulp is lacerated and the hemorrhage is encapsulated. As bleeding progresses the splenic capsule tears and produces massive hemorrhage. Sudden positional change, overzealous palpation, or even a cough may precipitate the latter.

The diagnosis of ruptured spleen was made preoperatively in this case, chiefly because of the development of signs indicating massive hemorrhage and shock in a patient whose history suggested repeated episodes of splenic infarction. The presence of the mycotic aneurysm as a cause of the rupture was not suspected.

Search for development of a mycotic aneurysm should be continued for at least several months following apparent cure, as well as during active infection. Paul and co-workers [38] have reported a case wherein the patient suddenly died from massive subarachnoid hemorrhage due to a ruptured mycotic aneurysm, occurring a month following onset of therapy. Blood cultures obtained during the course of treatment were all negative, as were postmortem cultures taken from the blood, heart valves, and the aneurysmal sac. In a similar case reported by Hurwitz and Arst [39] a symptomatic aneurysm of the brachial artery developed two weeks after cessation of therapy. The patient remained in good health after surgical resection of the aneurysm. No antibiotic therapy was given, since there was no evidence of recurrent infection. The patient described by Klein and Crowell [18] developed a mycotic aneurysm a week after the last positive blood culture and three weeks after the institution of antibiotic therapy. In the review of Cates and Christie,[21] there was apparent control of the infection in 13 of the 20 cases in which a ruptured mycotic aneurysm caused or contributed to death. Six of the patients died from cerebral hemorrhage from 4 to 16 weeks after the end of therapy. Another patient died from the same cause 22 months after apparent cure. A visible aneurysm regressed in two patients while they were receiving penicillin therapy. In two others receiving treatment the aneurysms progressed in size, in one case finally rupturing.

Although in the previously mentioned cases || cultures of the aneurysmal sacs were negative, Cates and Christie reported one case of apparent cure in which there was histological evidence of active inflammation and bacteria in the aneurysmal wall. Bacteria were not seen in the affected heart valves. With respect to these cases, it is noteworthy that progression of an aneurysm may occur despite eradication of the bacterial invaders. Once the infected embolus has been seeded and the internal elastic membrane destroyed, the basis for aneurysm is established.

## SUMMARY

A case is presented of subacute bacterial endocarditis and rupture of the spleen in a patient who recovered. Left upper quadrant pain and tenderness were prominent findings at the time of admission, and splenic infarcts were suspected. On the sixth day of antibiotic therapy, the patient suddenly displayed the symptoms and signs of massive intraperitoneal hemorrhage. At operation rupture of a mycotic aneurysm of the splenic artery was found.

This is apparently the 1st reported case of a rupture of the splenic artery associated with rupture of the spleen, and the 12th reported case of rupture of the spleen secondary to bacterial endocarditis.

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## CORRECTION

Through a mechanical error in correcting the type for the article, "Clinical Evaluation of Erythromycin" by Drs. Emitt H. Shoemaker and Ellard M. Yow, in the March issue of the Archives, page 397, the sense of the addendum was completely destroyed. The entire addendum should read as follows.

"Subsequent experience with the administration of erythromycin has confirmed the results reported in this paper. A patient with a staphylococcal bacteremia and meningitis has been treated with large doses of erythromycin, resulting in the sterilization of the blood stream but not the spinal fluid. This observation, along with the persistence of infection in empyema cavities reported in this paper, suggests that the diffusion of erythromycin across the serous membranes cannot always be relied upon. Erythromycin has also been used unsuccessfully in the treatment of another patient with overwhelming staphylococcal septicemia."

# News and Comment

## ANNOUNCEMENTS

**Residencies in Psychiatry.**—The Veterans Administration Hospital, Lyons, N. J., has available residencies in psychiatry for a one- to three-year period which are fully accredited by the American Board of Psychiatry and Neurology. The training program consists of lectures, conferences, and seminars under the direction of the Department of Psychiatry, New York Medical College, and offers intensive training, both intramurally and through rotation in special hospitals and clinics in the adjacent area. There is, in addition, an extensive series of guest lectures, as well as an Annual Institute at the hospital. Training may commence at any time.

**Fourth Middle East Medical Assembly.**—The Fourth Middle East Medical Assembly will be held at the Medical School of the American University in Beirut, Lebanon, April 9-11, under the direction of Dr. Hobart A. Reimann. Distinguished speakers from the Arab States, England, and the United States will participate, including Sir Lionel Whitby; Brigadier General Sam Seeley, United States Army; Captain A. R. Higgins, United States Navy; Colonel Robert Hoagland, United States Army; Dr. Richard Taylor, of the Rockefeller Foundation; Dr. Joseph McDonald, and others. Subjects of importance to the region will be discussed and illustrated in discussions and scientific exhibits.

**Eastern States Health Education Conference, 1954.**—The 1954 Eastern States Health Education Conference of The New York Academy of Medicine will be held at The New York Academy of Medicine, 2 East 103 St., New York, on Thursday and Friday, April 29 and 30, 1954. The program will include four sessions and an evening dinner meeting. The dinner meeting will be on Thursday evening.

The subject of this year's Conference will be Communication in Health Education. Health Education involves three major factors, namely, (*a*) goals or objectives, (*b*) motivation, and (*c*) communication.

Among the contributors to the Eastern States Health Education Conference are Professors William McPhee and Elihu Katz, of Columbia University Bureau of Applied Social Research; Dean Louis Hacker, of the School of General Studies at Columbia University; Dr. Leo Lowenthal, of the United States State Department Voice of America; Dr. Shirley A. Star, of the National Opinion Research Center, University of Chicago, and Prof. Earl Lomon Koos, of the School of Social Welfare, Florida State University.

Participation in the Conference is limited. Those interested in the Conference should address themselves to Iago Galdston, M.D., The New York Academy of Medicine, 2 East 103 St., New York 29.

**Third International Poliomyelitis Conference.**—The Third International Poliomyelitis Conference will be held Sept. 6-10, 1954, at the University of Rome, Orthopedic Clinic, Rome, Italy.

The Rome meetings are being sponsored jointly by the University of Rome (Italy), the High Commissionary of Hygiene and Health (Italy), the National Council on Research (Italy), the National Foundation for Maternity and Child Care (Italy), and the National Foundation for Infantile Paralysis (United States).

Prof. Carlo Marino Zuco, director of the orthopedic clinic of the University of Rome, is general chairman of the Conference. He plans to include presentation of 25 papers by physicians and scientists during eight sessions, covering acute medical care, infection, and immunity, orthopedics, physical medicine and rehabilitation, social aspects, and the trends in poliomyelitis. Each paper will be followed by a discussion session. In addition, there will be scientific and technical exhibits and clinical demonstrations.

Arrangements have been completed in the orthopedic clinic at the University of Rome for simultaneous interpretation of all the proceedings in French, Italian, German, Spanish, and English, so that the listener may have his choice of five languages. This system is similar to that employed by the United Nations.

Requests for hotel accommodations and other Conference information are available from the Secretariate of the Third International Poliomyelitis Conference, 6 via Lucullo, Rome, Italy. Cable address: inpolio, Rome.

**National Cancer Institute Grants-In-Aid.**—New support of the expanding search for chemical agents effective in the treatment of cancer is being given through grants-in-aid to scientists in universities and medical centers for research projects, it was announced today by Surgeon General Leonard A. Scheele, of the Public Health Service, United States Department of Health, Education, and Welfare.

The grants are administered by the National Cancer Institute. Dr. Scheele approved eight grants, totaling $704,563, for studies in chemotherapy of leukemia and allied forms of cancer. They were given as follows:

Dr. Sidney Farber, Children's Cancer Research Foundation, Boston, "Chemotherapy of Cancer," $50,000, and "Chemotherapy of Leukemia and Related Disorders," $150,000.

Dr. Alfred Gellhorn, Columbia University College of Physicians and Surgeons, New York, "Clinical and Laboratory Investigation in Cancer Chemotherapy," $141,255.

Dr. Ralph Jones, University of Pennsylvania, Philadelphia, "Chemotherapy of Leukemia and Allied Diseases," $85,800.

Dr. C. P. Rhoads, Sloan-Kettering Institute for Cancer Research, New York, "Expansion of Cancer Chemotherapy with Special Reference to Lymphomas and Leukemia," $200,000.

Dr. Byron E. Hall, Stanford University, California, "Studies on the Clinical, Cytologic, and Metabolic Effects of 6-Mercaptopurine and Other Chemotherapeutic Agents in Human Neoplasia," $17,460.

Dr. Thomas F. Dougherty, University of Utah, "Influence of Adrenocortical Hormones on Leukemogenesis," $18,036.

Dr. Maxwell M. Wintrobe, University of Utah, "Factors and Mechanisms Concerned in Hemopoiesis," $42,012.

A number of additional applications for grants are also under consideration.

Applications for research grants-in-aid are recommended to the Surgeon General for approval by the National Advisory Cancer Council, consisting of six professional and six lay members appointed from outside the Government. They are first passed upon by study sections, consisting of scientists qualified in the different fields of investigation.

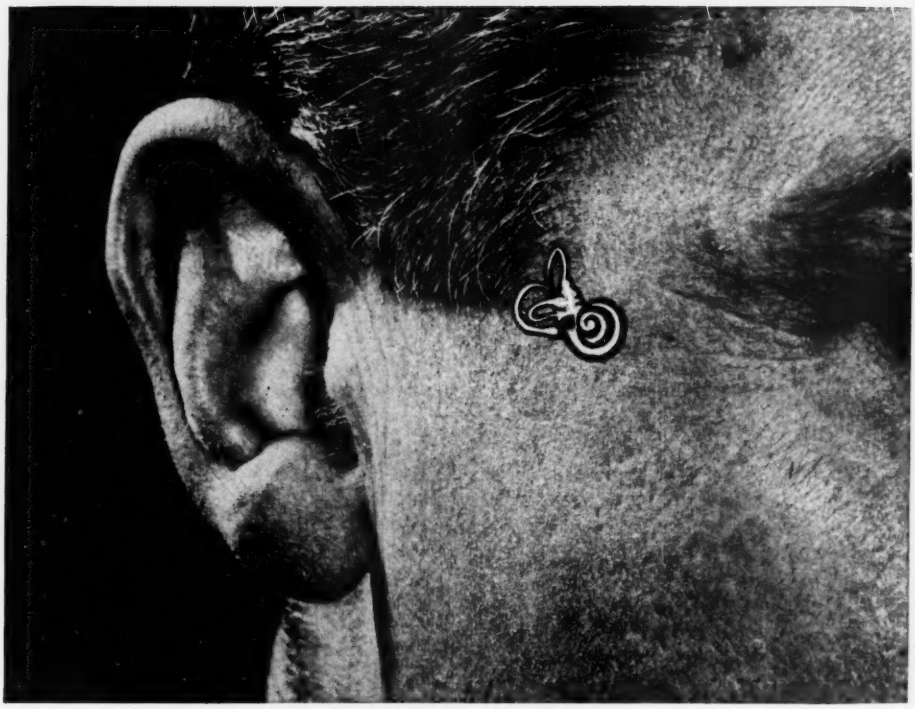
In connection with this strengthened research attack on cancer through chemotherapy, the Surgeon General also said that a committee of cancer chemotherapy investigations will be set up. This group will seek to integrate research through prompt interchange of information among investigators in this field.

**Regular Corps Examination for Medical Officers, United States Public Health Service.**—A competitive examination for appointment of Medical Officers to the Regular Corps of the United States Public Health Service will be held on June 1, 2, and 3, 1954. Examinations will be held at a number of points throughout the United States, located as centrally as possible in relation to the homes of candidates. Applications must be received no later than April 30, 1954.

The Regular Corps is a commissioned officer corps composed of members of various medical and scientific professions, appointed in appropriate categories such as medicine, dentistry, nursing, engineering, pharmacy, etc.

Appointments will be made in the grades of Assistant Surgeon (equivalent to Navy rank of Lieutenant, j.g.) and Senior Assistant Surgeon (equivalent to Lieutenant). In making assignments, consideration is given to the officer's preference, ability, and experience; however, all commissioned officers are subject to change of station and assignment as necessitated by the needs of the Service. Appointments are permanent in nature and provide opportunities to qualified physicians for a life career in clinical medicine, research, and public health. Applicants who successfully complete this examination may ordinarily expect appointment as soon as they become eligible.

Application forms and additional information may be obtained by writing to the Chief, Division of Personnel, Public Health Service, Department of Health, Education, and Welfare, Washington 25, D. C. Completed application forms must be received in the Division of Personnel no later than April 30, 1954. Applications received after that date may not be accepted and will be returned to the applicant.



*Through its probable action on the labyrinth, dependable control of vertigo and nausea has made Dramamine the most widely-prescribed product in its field.*

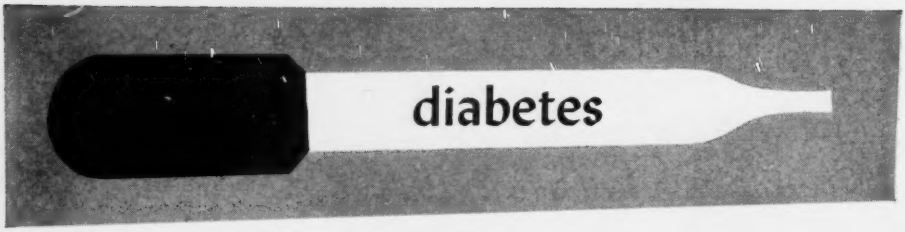
# Vertigo: The Labyrinthine Structure and Dramamine®

Dramamine's remarkable therapeutic efficiency is believed to be the result of suppression of the over-stimulated labyrinth. Thus it prevents the resulting symptom complex of vertigo, nausea and, finally, vomiting.

First known for its value in motion sickness, Dramamine is widely prescribed for nausea and vomiting of pregnancy, electroshock therapy, certain drugs and narcotization. It relieves vertigo of Ménière's syndrome, fenestration procedures, labyrinthitis, hypertensive disease and that accompanying radiation and antibiotic therapy.

A most impressive number of clinical studies shows that Dramamine has a high therapeutic index and minimal side actions. Drowsiness is possible in some patients but in many instances this side action is not undesirable.

Dramamine (brand of dimenhydrinate) is available in tablets of 50 mg. each; liquid containing 12.5 mg. per 4 cc. Dramamine is accepted by the Council on Pharmacy and Chemistry of the American Medical Association. G. D. Searle & Co., Research in the Service of Medicine.




**"the ideal detection center is the office of the family physician"[1]**

**Found:** 20,255 "new" diabetics in one year in the private practice of 5000 physicians responding to a nationwide poll.* Of these, 81% were detected by urine-sugar analysis; 62% of the physicians used *Clinitest.*

Only 19% of the diabetics in this survey were detected by findings other than glycosuria. "Every patient therefore should have at least one urinalysis as part of his examination, even if the purpose of his visit is only the removal of wax from the ears."[2]

# CLINITEST®

BRAND

**for detection of urine-sugar**

*Data from nationwide poll: Diabetes in daily practice

70% were over 40.
40% had a family history of diabetes.
65% were overweight.

1. Blotner, H., and Marble, A.: New England J. Med. *245*:567 (Oct. 11) 1951.
2. Steine, L.: GP *8*:45 (July) 1953.

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**Adjuncts in clinical management**

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Tablets: Boxes of 30 ( 5 gr.), bottles of 100
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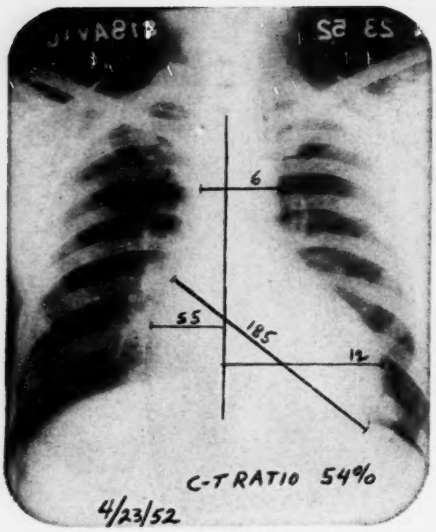
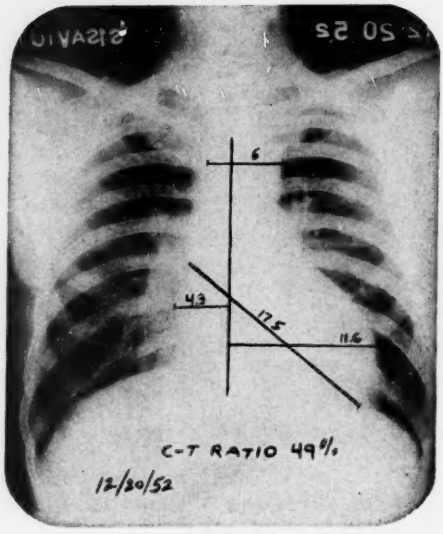



*Patient F.S. before Methium: Cardio-thoracic ratio 54%, blood pressure 240/160 mm. Hg.*[1]




*After Methium: Cardio-thoracic ratio 49%, blood pressure 160/100 mm. Hg. This patient (F.S.) experienced no toxic side effects and did not lose a single day of work.*[1]

## Functional improvement from stabilized, lower blood pressure

In the first few months of therapy, over 80 per cent of the patients treated with oral hexamethonium have had gradual reduction in mean blood pressure of 20 mm. Hg or more.[2,3] With continued treatment, up to or beyond a year, this reduction can often be maintained with no serious side effects and *no increase in dosage.*[3]

As blood pressure is reduced, and in some cases even without reduction, hypertension symptoms have regressed. Retinopathy may disappear, headache, cardiac failure and kidney function may improve.

Methium, a potent autonomic ganglionic blocking agent, reduces blood pressure by interrupting nerve impulses responsible for vasoconstriction. Because of its potency, careful use is required. Pretreatment patient-evaluation should be thorough. Special care is needed in impaired renal function, coronary artery disease and existing or threatened cerebral vascular accidents.

1. Kuhn, P. H.: Angiology 4:195 (June) 1953.
2. Moyer, J. H.; Snyder, H. B.; Johnson, I.; Mills, L. C., and Miller, S. I.: Am. J. M. Sc. *225*:379 (April) 1953.
3. Moyer, J. H.; Miller, S. I., and Ford, R. V.: J.A.M.A. *152*:1121 (July 18) 1953.

**Methium®**
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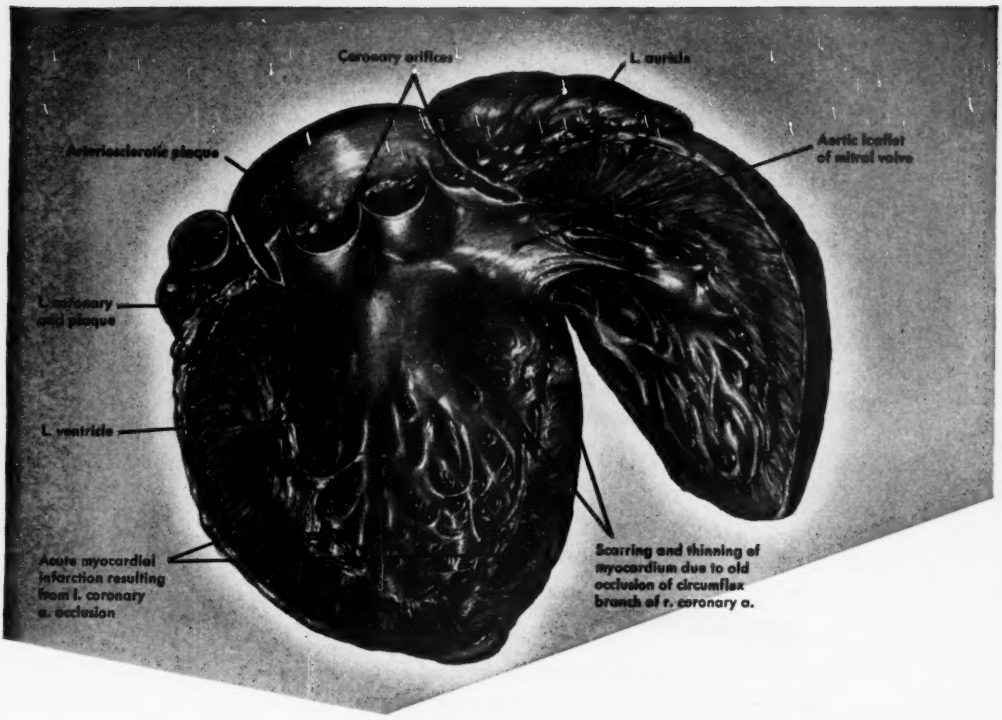
Coronary orifices
L. auricle
Arteriosclerotic plaque
Aortic leaflet of mitral valve
L. coronary artery plaque
L. ventricle
Acute myocardial infarction resulting from l. coronary a. occlusion
Scarring and thinning of myocardium due to old occlusion of circumflex branch of r. coronary a.

# Myocardial Infarction with Severe Shock:

*Reduction of Mortality*

"... in correcting the state of shock we have enabled certain patients to recover from the initial episode, which otherwise gave every indication of culminating in death."[1]

Levophed infusion causes a striking rise in oxygen tension in areas of myocardial ischemia produced by coronary obstruction.[2] "It is therefore reasonable to suppose that the restoration of arterial pressure to a level consistent with an adequate coronary flow must limit the size of the infarct, save healthy myocardium, shorten the period of shock, and lessen the likelihood of congestive failure at a later date."[3]

"Severe cardiogenic shock demands therapy... the most efficacious method of treatment now available is use of vasopressor drugs."[4] "Current usage favors nor-epinephrine."[5]

**References:**

1. Kurland, G. S., and Malach, Monte: *New England Jour. Med.*, 247:383, Sept. 11, 1952.
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5. Levine, H. D., and Levine, S. A.: *Med. Clin. North America*, 37:955, July, 1953.

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**BITARTRATE**

Brand of Levarterenol bitartrate *(nor-epinephrine)*

**THE MOST POWERFUL PRESSOR ANTIDOTE FOR**

*Shock*

Supplied: Levophed bitartrate solution 0.2 per cent (equivalent to 0.1 per cent base), ampuls of 4 cc., boxes of 10. (Each 4 cc. to be administered in 1000 cc. of 5 per cent dextrose.)

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## in arthritis
## and allied disorders

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potent, non-hormonal antiarthritic agent

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| Gouty Arthritis | Rheumatoid Arthritis |
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**Painful Shoulder (including peritendinitis, capsulitis, bursitis, and acute arthritis)**

Since BUTAZOLIDIN is a potent agent, patients for therapy should be selected with care; dosage should be judiciously controlled; and the patient should be regularly observed so that treatment may be discontinued at the first sign of toxic reaction.

Physicians unfamiliar with the use of BUTAZOLIDIN are urged to send for complete descriptive literature before employing it.

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*Lester M. Morrison, M.D., Los Angeles, in Rev. Gastroenterology, 20:744 (Oct.) 1953; abstract in J.A.M.A. 153:1580 (Dec. 26) 1953.*

* *now available under the name*

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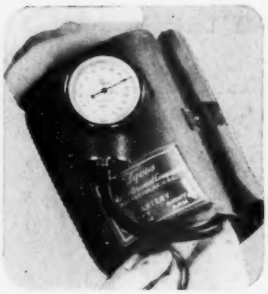

*for the patient with moderate or severe essential hypertension*

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progressive relief of hypertensive symptoms if present.

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benefits in up to 80% of cases: e.g., hypertension gradually reduced, renal circulation improved, eye-ground changes may be reversed.

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therapy is generally well tolerated with initial low dosages, gradually increased.[1,2,3] Patient response is the guide to dosage adjustment.[4] Optimal maintenance dosage level is usually reached only after 3 weeks or more; marked therapeutic effect cannot be expected with initial low dosages.[4]


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